

**Public Assessment Report**

**Decentralised Procedure**

**CORIPREN**

**20 mg/20 mg film coated tablets**

**(enalapril maleate, lercanidipine hydrochloride)**

**APPLICANT**

**Recordati Industria Chimica e Farmaceutica S.p.A.**

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**20148 Milan – Italy**

**IT Marketing Authorisation Number: 038568**

**Procedure number: IT/H/0266/003/DC**

**TABLE OF CONTENTS**

Module 1: Information about the initial procedure Page 3

Module 2: Summary of Product Characteristics Page 4

Module 3: Package Leaflets Page 25

Module 4: Labelling Page 32

Module 5: Scientific discussion during the initial procedure Page 35

I Introduction Page 35

II About the product Page 36

III Scientific Overview and discussion Page 37

III.1 Quality aspects Page 37

III.2 Non-clinical aspects Page 41

III.3 Clinical aspects Page 41

IV Overall conclusions and benefit-risk assessment Page 43

**Module 1**

**Information about the Initial Procedure**

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| **Product Name** | **IT/H/0266/003/DC:**  20mg/20mg film coated tablets  (enalapril maleate, lercanidipine hydrochloride) |
| **Type of application** | Decentralised procedure according to Article 28(3) and Article 10b (fixed combination application) of Directive 2001/83/EC) |
| **Active Substance** | enalapril maleate, lercanidipine hydrochloride |
| **Form** | Film coated tablets |
| **Strength** | 20mg/20mg |
| **MA Holder** | Recordati Industria Chimica e Farmaceutica S.p.A.,  Via M. Civitali 1, 20148 Milan – Italy |
| **Reference Member State (RMS)** | IT |
| **Concerned Memember States (CMS)** | ES |
| **Procedure number** | IT/H/0266/003/DC |
| **Timetable** | End of procedure: Day 150 – 26 November 2014 |

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the SMPC approved at European level.

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1. NAME OF THE MEDICINAL PRODUCT**

Coripren 20 mg/20 mg film-coated tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 20 mg enalapril maleate (equivalent to 15.29 mg enalapril) and 20 mg lercanidipine hydrochloride (equivalent to 18.88 mg lercanidipine).

Excipient with known effects: Each tablet contains lactose monohydrate. 204 mg

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablet.

Orange, circular , biconvex, tablets of 11 mm.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled with enalapril 20 mg lercanidipine 20 mg and given concurrently as separate tablets.

**4.2 Posology and method of administration**

Posology

The recommended dose is one tablet once a day at least 15 minutes before a meal.

*Elderly patients****:***

The dose should depend on the patient's renal function (see "Use in renal impairment").

*Patients with renal impairment:*

Coripren is contraindicated in patients with severe renal dysfunction (creatinine clearance <30 ml/min) or in patients undergoing haemodialysis (see section 4.3 and 4.4). Particular caution is needed when initiating treatment in patients with mild to moderate renal dysfunction.

*Patient with hepatic impairment:*

Coripren is contraindicated in severe hepatic dysfunction. Particular caution is needed when initiating treatment in patients with mild to moderate hepatic dysfunction.

*Paediatric population:*

There is no relevant use of Coripren in the paediatric population in the indication of hypertension.

Method of administration

Precautions to be taken before handling or administering the medicinal product:

* Treatment should be preferably administered in the morning at least 15 minutes before breakfast.
* This product should not been administered with grapefruit juice (see section 4.3 and 4.5).

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Coripren must not be taken in:

* Hypersensitivity to any ACE-inhibitor or dihydropyridine calcium channel blocker or to any other constituent of this medicinal product
* History of angioedema associated with ACE-inhibitor therapy
* Hereditary or idiopathic angioedema
* Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
* Left ventricular outflow obstruction, including aortic stenosis
* Untreated congestive heart failure
* Unstable angina pectoris
* Within one month of a myocardial infarction
* Severe renal impairment (creatinine clearance < 30 ml/min), including patients undergoing haemodialysis
* Severe hepatic impairment
* Co-administration with:
* strong CYP3A4 inhibitors (see section 4.5)
* cyclosporin (see section 4.5)
* grapefruit juice (see section 4.5)

The concomitant use of Coripren with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).

**4.4 Special warnings and precautions for use**

Symptomatic hypotension

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, symptomatic hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see section 4.5). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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.

Sick-sinus syndrome

Particular caution is recommended in the use of lercanidipine in patients with sick-sinus syndrome (without a pacemaker).

Left ventricular dysfunction and ischaemic heart disease

Although haemodynamic controlled studies revealed no impairment of ventricular function, caution must be exercised when treating patients with left ventricular dysfunction with calcium channel blockers. It has been suggested that patients with ischaemic heart disease show an elevated cardiovascular risk under treatment with some short-acting dihydropyridines. Although lercanidipine is long-acting, caution is advised in these patients.

In rare cases, some dihydropyridines can cause precordial pain or angina pectoris. Very rarely, patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed (see section 4.8).

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 are part of the normal medical practice for these patients.

Renal failure has been reported in association with enalapril, mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognized promptly and treated appropriately, renal failure when associated with therapy with 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

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitor. 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, cautious titration and monitoring of renal function.

Kidney transplantation

There is no experience in the use of lercanidipine or enalapril in patients who have recently undergone kidney transplantation. Treatment with Coripren is therefore not recommended.

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.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol, procainamide or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed severe infections which in few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any signs of infection.

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx, has been reported in patients treated with ACE-inhibitors, including enalapril. This may occur at any time during treatment. In such cases, enalapril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. 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.

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.

Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3ml to 0.5ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (Also see section 4.3.)

Anaphylactoid Reactions during Hymenoptera Desensitization

Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitization.

Anaphylactoid Reactions during LDL Apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Hypoglycemia

Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor, should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See section 4.5.)

Cough

Cough has been reported with the use of ACE-inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE-inhibitor-induced cough should also be considered as part of the differential diagnosis of cough.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory rennin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalemia include 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; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). 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. Hyperkalemia 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.

Inducers of CYP3A4

CYP3A4 inducers such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin can reduce serum levels of lercanidipine so that the efficacy of the drug can be lower than expected (see section 4.5).

Ethnic differences

As with other ACE-inhibitors, enalapril is apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because plasma renin levels are often lower in the black hypertensive population.

Pregnancy

Coripren 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 sections 4.3 and 4.6).

The use of lercanidipine is also not recommended during pregnancy or in women who might become pregnant (see section 4.6)

Lactation

The use of Coripren is not recommended during lactation (see section 4.6).

Paediatric population

The safety and efficacy of this association has not been demonstrated in children.

Alcohol

Alcohol should be avoided because it may potentiate the effect of vasodilator antihypertensives (see section 4.5).

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Coripren.

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

The antihypertensive effect of Coripren could be potentiated by other blood pressure-lowering drugs such as diuretics, beta-blockers, alpha-blockers and other substances.

In addition, the following interactions have been observed with one or other constituents of the combined product.

***Enalapril maleate***

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

“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).”

Potassium sparing diuretics or 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. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

Diuretics (thiazide or loop diuretics)

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

Other antihypertensive agents

Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

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 further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Tricyclic antidepressants/Antipsychotics/Anesthetics/Narcotics

Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 (COX-2) Inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other 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.

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.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

(See sections 4.4 and 4.8)

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetyl salicylic acid, thrombolytics and β‑blockers

Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β‑blockers.

***Lercanidipine***

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 section 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 Cmax of the eutomer S-lercanidipine).

Cyclosporin

Cyclosporin and lercanidipine must not be used together (see section 4.3).

Increased plasma concentrations of both drugs have been observed following concurrent administration. A study in healthy young volunteers showed no changes in plasma lercanidipine levels when cyclosporin was taken 3 hours after ingestion of lercanidipine, but the AUC of cyclosporin rose by 27%. Co-administration of lercanidipine with cyclosporin caused a 3-fold rise in plasma lercanidipine levels and a 21% increase in AUC of cyclosporin.

Grapefruit juice

Lercanidipine should not be taken with grapefruit juice (see section 4.3).

As for other dihydropyridines, the metabolism of lercanidipine can be inhibited by the ingestion of grapefruit juice, resulting in a rise in the systemic availability of lercanidipine and increased hypotensive effect.

Alcohol

Alcohol should be avoided since it may potentiate the effect of vasodilator antihypertensives (see section 4.4).

Substrates of CYP3A4

Caution is required on the co-prescribing of lercanidipine with other substrates of CYP3A4 such as terfenadine, astemizole, Class III antiarrhythmics, e.g. amiodarone, quinidine.

Inducers of CYP3A4

Concurrent use of lercanidipine with CYP3A4 inducers such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin should be approached with caution, because the antihypertensive effect of lercanidipine can be reduced. Blood pressure must therefore be monitored more frequently than usual.

Digoxin

Co-administration of 20 mg lercanidipine in patients chronically treated with ß-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin after administration of 20 mg lercanidipine showed a mean increase in digoxin Cmax of 33%, whereas neither AUC nor renal clearance were significantly altered. Patients on concomitant digoxin should be closely monitored for clinical signs of digoxin toxicity.

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 (tmax 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 ß-adrenergic receptors.

Cimetidine

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but caution is required at higher doses since the bioavailability of lercanidipine, and therefore its hypotensive effect, may be increased.

Fluoxetine

An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in healthy volunteers aged 65 ± 7 years (mean ± s.d.), showed no clinically relevant modification of the pharmacokinetics of lercanidipine.

Simvastatin

When a 20 mg dose of lercanidipine was repeatedly co-administered with 40 mg of simvastatin, the AUC of lercanidipine was not significantly modified, whereas the AUC of simvastatin increased by 56% and that of its principal active metabolite, ß-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected if lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such a drug.

Warfarin

Co-administration of 20 mg lercanidipine to fasted healthy volunteers did not alter the pharmacokinetics of warfarin.

**Paediatric population**

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

*For enalapril*

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative 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 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. Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

*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 with childbearing potential unless effective contraception is used.

*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).

Coripren 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.

Breast-feeding

*For enalapril*

Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Enalapril 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 Enalapril 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 Coripren should not be used during breast-feeding.

Fertility

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by channel blockers. In cases where repeated in-vitro fertilisation is unsuccessful and where another explanation cannot be found, the possibility of calcium channel blockers as the cause should be considered.

**4.7 Effects on ability to drive and use machines**

Coripren has minor influence on the ability to drive and use machines. However, caution is advised because dizziness, asthenia, fatigue and in rare cases somnolence may occur (see section 4.8).

**4.8 Undesirable effects**

Summary of the safety profile

The safety of Coripren 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 Coripren at a dose of 10mg/10mg, 20mg/10mg and 20mg/20mg. 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 Coripren were cough (4.03%), dizziness (1.67%) and headache (1.67%).

Tabulated summary of adverse reactions

In the table below, adverse reactions reported in clinical studies with Coripren 10mg/10mg, 20mg/10mg and 20mg/20mg and for which a reasonable causal relationship exists are listed by MedDRA system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) not known (frequency cannot be estimated from the available data).

|  |  |
| --- | --- |
| **Blood and lymphatic system disorders** | |
| Uncommon: | Thrombocytopenia |
| Rare | Haemoglobin decreased |
| **Immune System Disorders** | |
| Rare: | Hypersensitivity |
| **Metabolism and nutrition disorders** | |
| Uncommon | Hyperkaliemia |
| **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, oropharingeal 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 |
| **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.*

Description of selected adverse reactions

The incidence of selected listed adverse reactions frequently observed with enalapril and lercanidipine monotherapies, is shown in the table below, as reported in a double-blind, randomized, factorial clinical study:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Placebo (n=113) | E20 (n=111) | L20 (n=113) | E20/L20 (n=116) |
| Subject with any ADR | 5.3% | 10.8% | 8.8% | 8.6% |
| Cough | 1.8% | 3.6% | - | 1.7% |
| Dizziness | - | 1.8% | - | 0.9% |
| Headache | 0.9% | 0.9% | 1.8% | 0.9% |
| Oedema peripheral | 0.9% | - | 1.8% | - |
| Tachycardia | - | 1.8% | 3.5% | 0.9% |
| Palpitations | - | 0.9% | 0.9% | - |
| Flushing | - | - | 1.8% | 0.9% |
| Rash | - | 0.9% | 0.9% | - |
| Fatigue | - | - | - | 0.9% |

Additional information on the individual components.

Adverse reactions reported with one of the individual components (enalapril or lercanidipine) may be potential undesirable effect with Coripren as well, even if not observed in clinical trials or during the post-marketing period.

*Enalapril alone*

Among the adverse drug reactions reported for enalapril are:

*Blood and the lymphatic system disorders:*

uncommon: anemia (including aplastic and hemolytic)

rare: neutropenia, decreases in hemoglobin, decreases in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases

*Endocrine disorders:*

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

*Metabolism and nutrition disorders:*

uncommon: hypoglycemia (see section 4.4)

*Nervous system and psychiatric disorders:*

common: headache, depression

uncommon: confusion, somnolence, insomnia, nervousness, paresthesia, vertigo

rare: dream abnormality, sleep disorders

*Eye disorders:*

very common: blurred vision

*Cardiac and vascular disorders:*

very common: dizziness

common: hypotension (including orthostatic hypotension), syncope, chest pain, rhythm disturbances, angina pectoris, tachycardia

uncommon: orthostatic hypotension, 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.

*Respiratory, thoracic and mediastinal disorders:*

very common: cough

common: dyspnea

uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma

rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia

*Gastrointestinal disorders:*

very common: nausea,

common: diarrhea, abdominal pain, taste alteration

uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer

rare: stomatitis/aphthous ulcerations, glossitis

very rare: intestinal angioedema

*Hepatobiliary disorders:*

**rare: hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)**

*Skin and subcutaneous tissue disorders:*

common: rash, hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4)

uncommon: diaphoresis, pruritus, urticaria, alopecia

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

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

*Renal and urinary disorders:*

uncommon: renal dysfunction, renal failure, proteinuria

rare: oliguria

*Reproductive system and breast disorders:*

uncommon: impotence

rare: gynecomastia

*General disorders and administration site conditions:*

very common: asthenia

common: fatigue

uncommon: muscle cramps, flushing, tinnitus, malaise, fever

*Investigations:*

common: hyperkalemia, increases in serum creatinine

uncommon: increases in blood urea, hyponatremia

rare: elevations of liver enzymes, elevations of serum bilirubin

*Lercanidipine alone*

The adverse drug reactions most commonly reported in controlled clinical trials were headache, dizziness, oedema peripheral, tachycardia, palpitations and flushing, with each occurring in less than 1% of patients.

*Immune system disorders*

very rare: hypersensitivity

*Psychiatric disorders*

rare: somnolence

*Nervous system disorders*

uncommon: headache, dizziness

*Cardiac disorders*

uncommon: tachycardia, palpitations

rare: angina pectoris

*Vascular disorders*

uncommon: flushing

very rare*:* syncope

*Gastrointestinal disorders*

rare: nausea, dyspepsia, diarrhoea, abdominal pain, vomiting

*Skin and subcutaneous tissue disorders*

rare: rash

*Musculoskeletal and connective tissue disorders*

rare: myalgia

*Renal and urinary disorders*

rare: polyuria

*General disorders and administration site conditions*

uncommon: oedema peripheral

rare: asthenia, fatigue

From spontaneous reports in post-marketing experience, the following adverse reactions have been reported very rarely (<1/10,000): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.

Some dihydropyridines may rarely lead to precordial localised pain or angina pectoris. Very rarely, patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may occur.

Lercanidipine does not appear to have any adverse effect on blood sugar or serum lipid levels.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V\*.

**4.9 Overdose**

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 marketed 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.

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 PROPERTIES**

* 1. **Pharmacodynamic properties**

Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers: enalapril and lercanidipine.

ATC code: C09BB02

Coripren is the fixed combination of an ACE-inhibitor (enalapril) and a calcium channel blocker (lercanidipine), two antihypertensive compounds with complementary mechanism of action to control blood pressure in patients with essential hypertension.

Enalapril

Enalapril maleate is the maleate salt of enalapril, a derivative of two aminoacids, L-alanine and L-proline. Angiotensin-converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the vasopressor agent angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to the removal of negative feedback of renin release) and decreased aldosterone secretion.

Since ACE is identical to kininase II, enalapril may also inhibit the degradation of bradykinin, a potent vasodepressor peptide. However the role of this mechanism in the therapeutic effects of enalapril is still not understood.

Although the mechanism by which enalapril reduces blood pressure is primarily attributed to suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low renin levels.

Administration of enalapril to hypertensive patients reduces both supine and standing blood pressure, without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity normally occurs 2 to 4 hours after oral administration of a single dose of enalapril. Onset of the antihypertensive action was usually seen after one hour with maximum reduction of blood pressure observed 4 to 6 hours after administration. The duration of action is dose-related, but with recommended doses, antihypertensive and haemodynamic effects have been shown to persist for at least 24 hours.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

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.

Lercanidipine

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of the antihypertensive action is based on a direct relaxant effect on vascular smooth muscle, thus lowering total peripheral resistance. Despite its short pharmacokinetic plasma half-life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity

Since the vasodilatation produced by lercanidipine has a gradual onset, acute hypotension with reflex tachycardia has only been rarely observed in hypertensive patients.

As with other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Enalapril/Lercanidipine

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

* Coripren 10mg/10mg

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.

* Coripren 20mg/10mg

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.

* Coripren 20mg/20mg

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%).

* 1. **Pharmacokinetic properties**

No pharmacokinetic interactions have been observed on concurrent administration of enalapril and lercanidipine.

Pharmacokinetics of enalapril

*Absorbtion*

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The absorption of oral enalapril is not affected by the presence of food in the gastrointestinal tract.

*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.

Over the range of concentrations which are therapeutically relevant, enalapril binding to human plasma proteins does not exceed 60%.

*Biotransformation*

Apart from the conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

*Elimination*

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and unchanged enalapril (about 20%).

*Renal impairment*

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 dialysys 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.

Pharmacokinetics of lercanidipine

*Absorption*

Lercanidipine is completely absorbed after oral administration and peak plasma levels are reached after approximately 1.5 - 3 hours.

The two enantiomers of lercanidipine show a similar plasma level profile: the time to peak plasma concentration is the same and the peak plasma concentration and AUC are, on average 1.2 times higher for the (S)-enantiomer. The elimination half-lives of the two enantiomers are essentially the same. No interconversion of the two enantiomers is observed "in vivo".

Due to the high first-pass metabolism, the absolute bioavailability of oral lercanidipine in non-fasted conditions is about 10%. However, the bioavailability on ingestion by healthy volunteers under fasting conditions is reduced to 1/3.

Oral availability of lercanidipine increases 4-fold when it is ingested up to 2 hours after a high-fat meal. Hence the drug should be taken before meals.

*Distribution*

Distribution from plasma into tissues and organs is rapid and extensive.

The degree of plasma protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be higher.

*Biotransformation*

Lercanidipine is extensively metabolised by CYP3A4; no parent substance is found either in urine or faeces. It is predominantly converted into inactive metabolites and approximately 50% of the dose is excreted in the urine.

*In vitro* experiments with human liver microsomes have demonstrated that lercanidipine shows slight inhibition of the two enzymes CYP3A4 and CYP2D6 at concentrations 160- and 40-times higher than the peak plasma levels achieved after administration of the 20 mg dose.

Furthermore, interaction studies in humans have shown that lercanidipine does not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, at therapeutic doses, lercanidipine is not expected to inhibit the biotransformation of drugs metabolised by CYP3A4 or CYP2D6.

*Elimination*

Elimination essentially occurs through biotransformation.

A mean terminal elimination half-life of 8-10 hours was calculated, and due to the high binding to lipid membranes, therapeutic activity lasts for 24 hours. No accumulation was shown after repeated administration.

*Linearity/non-linearity*

Oral administration of lercanidipine results in plasma levels that are not directly proportional to the dose (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations were in the ratio of 1:3:8 and areas under the plasma concentration-time curves in the ratio of 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

*Additional information on special populations*

It has been shown that the pharmacokinetic behaviour of lercanidipine in elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment is similar to that observed in the general patient population. Patients with severe renal dysfunction or dialysis-dependent patients showed higher concentrations of the drug (approximately 70%). In patients with moderate to severe hepatic impairment, systemic bioavailability of lercanidipine is probably increased because the drug is normally extensively metabolised in the liver.

**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.

The following data exist for the two individual components, enalapril and lercanidipine.

Enalapril

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

Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and is excreted in milk. Angiotensin converting enzyme 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.

Lercanidipine

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

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.

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.

**6. PHARMACEUTICAL PARTICULARS**

* 1. **List of excipients**

*Core:*

Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycolate (Type A)

Povidone K30

Sodium hydrogen carbonate

Magnesium stearate

*Film-Coating:*

Hypromellose 5 cP

Titanium dioxide (E171)

Macrogol 6000

Iron oxide yellow (E172)

Talc

Iron oxide red (E172)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years.

**6.4 Special precautions for storage**

Store in the original package in order to protect from light and moisture. Do not store above 25°C.

**6.5 Nature and contents of container**

Polyamide-aluminium-PVC/aluminium blister

Packs of 7, 14, 28, 30, 35, 42, 50, 56, 90, 98 and 100 tablets.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal <and other handling>**

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

**7. MARKETING AUTHORISATION HOLDER**

RECORDATI Industria Chimica e Farmaceutica S.p.A. – Via Matteo Civitali 1, I-20148 Milan, Italy

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the PIL approved at European level.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Coripren 20 mg/20 mg film-coated tablets**

Enalapril maleate/Lercanidipine hydrochloride

|  |
| --- |
| **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**   1. Keep this leaflet. You may need to read it again. 2. If you have any further questions, ask your doctor or pharmacist. 3. This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. 4. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. |

**What is in this leaflet**:

1. What Coripren is and what it is used for

2. What you need to know before you take Coripren

3. How to take Coripren

4. Possible side effects

5. How to store Coripren

6. Contents of the pack and other information

**1. What Coripren is and what it is used for**

Coripren is a fixed combination of an ACE-inhibitor (enalapril maleate) and a calcium channel blocker (lercanidipine hydrochloride), two medicines that lower blood pressure.

Coripren is used to treat high blood pressure (hypertension) in adult patients who are currently taking enalapril and lercanidipine as separate tablets.

1. **What you need to know before you take Coripren**

**Do not take Coripren:**

* If you are allergic to enalapril or lercanidipine or any of the other ingredients of this medicine (listed in Section 6).
* If you have ever had an allergic reaction to a type of medicine similar to those contained in Coripren, i.e. medicines called ACE-inhibitors or calcium channel blockers.
* If you have ever had swelling of your face, lips, mouth, tongue or throat which caused difficulty in swallowing or breathing (angioedema) after taking a type of medicine called ACE-inhibitors, or when the reason why was not known or it was inherited.
* If you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskirenIf you are more than 3 months pregnant (it is also better to avoid Coripren in early pregnancy – see Pregnancy section).
* If you suffer from certain heart diseases:
* obstruction to the flow of blood out of the heart, including a narrowing of the aortic valve in your heart
* untreated heart failure
* chest discomfort occurring at rest or becoming worse or happening more often (unstable angina)
* within one month of a heart attack.
* If you have severe kidney problems, or if you are undergoing dialysis.
* If you have severe liver problems
* If you are taking drugs that are inhibitors of the hepatic metabolism, such as:
* antifungals (e.g. ketoconazole, itraconazole).
* macrolide antibiotics (e.g. erythromycin, troleandomycin).
* antivirals (e.g. ritonavir).
* If you are taking another drug called cyclosporin or ciclosporin (used after transplants to prevent organ rejection).
* With grapefruit or grapefruit juice.

**Warnings and precautions**

Talk to your doctor or pharmacist before taking Coripren:

* If you have low blood pressure (you may notice this as faintness or dizziness, especially when standing).
* If you have been very sick (excessive vomiting) or had had diarrhoea recently.
* If you are on a salt restricted diet.
* If you have a heart problem.
* If you have a condition involving the blood vessels in the brain.
* If you have a kidney problem (including kidney transplantation).
* If you have a liver problem.
* If you have a blood problem, such as low or lack of white blood cells (leucopenia, agranulocytosis), low platelet count (thrombocytopenia or a decreased number of red blood cells (anemia).
* If you have a collagen vascular disease (e.g. lupus erithematosus, rheumatoid arthritis or scleroderma)
* If you are a black patient you should be aware that black patients are at increased risk of allergic reactions with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing when taking ACE-inhibitors.
* If you have diabetes.
* If you develop a persistent dry cough.
* If you are taking potassium supplements, potassium-sparing agents, or potassium-containing salt substitutes.
* If you have an intolerance to certain sugars (lactose)
* If you are taking any of the following medicines used to treat high blood pressure:

- an angiotensin II receptor blocker (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems.

- aliskiren

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Coripren”.

If you are about to have a procedure

If you are about to have any of the following, tell your doctor that you are taking Coripren:

* any surgery or receive anaesthetics (even at the dentist)
* a treatment to remove cholesterol from your blood called “LDL apheresis”
* a desensitization treatment, to lower the effect of any allergy to bee or wasp stings.

You must tell your doctor if you think you are (or might become) pregnant or breast-feeding (see pregnancy, breast-feeding and fertility section).

**Children and adolescents**

Do not give this medicine to children and adolescents under the age of 18 years as there is no information on if it works and if it is safe.

**Other medicines and Coripren**

Coripren must not be taken with certain medications.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because when Coripren is taken with certain other medicines, the effect of Coripren or of the other medicine may be changed, or certain side effects may occur more frequently.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

* medicines containing potassium (including dietary salt substitutes)
* other medicines that lower blood pressure, such as diuretics (water pills)
* lithium (a medicine used to treat a certain kind of depression)
* medicines for depression called ‘tricyclic antidepressants’
* medicines for mental problems called ‘antipsychotics’
* non-steroidal anti-inflammatory drugs, including COX-2-inhibitors (medicines that reduce inflammation and can be used to help relieve pain)
* certain pain or arthritis medicines including gold therapy
* certain cough and cold medicines and weight reducing medicines which contain something called a ‘sympathomimetic agent’
* medicines for diabetes (including oral antidiabetic medicines and insulin) astemizole or terfenadine (medicines for allergies)
* amiodarone or quinidine (medicines to treat a fast heart beat)
* phenytoin or carbamazepine (medicines for epilepsy)
* rifampicin (a drug for the treatment of tuberculosis)
* digoxin (a medicine to treat heart problems)
* midazolam (a medicine that helps you to sleep)
* beta-blockers (medicines to treat high blood pressure and heart problems)
* a medicine for ulcers and heartburn called cimetidine at daily doses of more than 800 mg

“Your doctor may need to change your dose and/or to take other precautions:

If you are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings “Do not take Coripren” and “Warnings and precautions”)”

**Coripren with food, drink and alcohol**

* Coripren should be taken at least 15 minutes before a meal.
* Alcohol can increase the effect of Coripren. You are therefore advised either to consume no alcohol or to strictly limit your alcohol intake.
* Coripren should not be taken with grapefruit or grapefruit juice.

**Pregnancy, breast-feeding and fertility**

Pregnancy and fertility

You must tell your doctor if you think you are (or might become) pregnant. Coripren is not recommended in women who might become pregnant and in early pregnancy and must not be taken when you are more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast­feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking Coripren. In the case of an older baby your doctor should advise you on the benefits and risks of taking Coripren whilst breast-feeding, compared with other treatments.

**Driving and using machines**

If you develop dizziness, weakness, tiredness or drowsiness during treatment with this medicine, you must not drive a vehicle or operate machines.

**Coripren contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

**3. How to take Coripren**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**Adults**: unless otherwise prescribed by your doctor, the recommended dose is one tablet once daily at the same time each day. The tablet should preferably be taken in the morning at least 15 minutes before breakfast. The tablets should be swallowed whole with water.

**Patients with kidney problems/elderly:** your dose of medicine will be decided by your doctor

and will be based on how well your kidneys are working.

**If you take more Coripren than you should**

If you have taken more Coripren than you should, talk to your doctor or go to the hospital straight away. Take the medicine pack with you. Taking more than the correct dose can cause an excessive drop in blood pressure and your heart can beat irregularly or faster.

**If you forget to take Coripren**

* If you forget to take your tablet, skip the missed dose.
* Take the next dose as usual.
* Do not take a double dose to make up for the forgotten dose.

## If you stop taking Coripren

* Do not stop taking your medicine unless your doctor tells you to.
* If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, Coripren can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Some side effects can be serious.**

**If any of the following happen, tell your doctor straight away:**

* Allergic reaction with swelling of your face, lips, tongue or throat which may cause difficulty in breathing or swallowing;

When you start taking Coripren you might feel faint or dizzy or have blurred vision; this is caused by a sudden fall in blood pressure and if this happens, it will help to lie down. If you are worried, please talk to your doctor.

**Side effects observed with Coripren**

Common (may affect up to 1 in 10 people)

Cough, feeling dizzy, headache.

Uncommon(may affect up to 1 in 100 people)

Changes in blood values such as a lower number of blood platelets, increased blood potassium level, nervousness (anxiety), feeling dizzy when standing up, vertigo, fast heartbeat, fast or uneven heartbeat (palpitations), sudden reddening of your face, neck or upper chest (flushing), low blood pressure, abdominal pain, constipation, feeling sick (nausea), higher levels of liver enzymes, redness of the skin, joint pain, increased number of times one urinates, feeling weak, tiredness, feeling hot, ankle swelling.

Rare(may affect up to 1in 1,000 people)

Anaemia, allergic reactions, ringing in your ears (tinnitus), fainting, dry throat, sore throat, indigestion, salty sensation on the tongue, diarrhoea, dry mouth, swelling of gums, allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing, skin rash, hives, getting

up at night to urinate, producing large amounts of urine, impotence.

**Additional side effects observed with enalapril or lercanidipine alone**

**Enalapril**

Very Common(affects more than 1 in 10 people)

Blurred vision.

Common (affects less than 1 in 10 people)

depression, chest pain, changes in heart rhythm, angina, shortness of breath, change in sense of taste, increased levels of creatinine in your blood (usually detected by a test).

Uncommon(affects less than 1 in 100 people)

Anaemia (including aplastic and haemolytic), sudden fall in blood pressure, confusion, sleeplessness or sleepiness, feeling your skin prickling or being numb, heart attack (possibly due to very low blood pressure in certain high-risk patients, including those with blood flow problems of the heart or brain), stroke (possibly due to very low blood pressure in high-risk patients), runny nose, sore throat and hoarseness, asthma, slow movement of food through your intestine, inflammation of your pancreas, being sick, irritated stomach (gastric irritations), ulcer, anorexia, increased perspiration, itching or nettle rash, loss of hair, impaired kidney function, kidney failure, high level of proteins in your urine (measured in a test), muscle cramps, generally feeling unwell (malaise), high temperature (fever), low level of blood sugar or sodium, high level of blood urea (all measured in a blood test).

Rare(affects less than 1 in 1,000 people)

Changes in blood values such as a lower number of white blood cells, bone marrow depression, autoimmune diseases, strange dreams or sleep problems, ‘Raynaud’s phenomenon’ (where your hands and feet may become very cold and white due to low blood flow), pulmonary infiltrates, inflammation of your nose, pneumonia, liver problems such as lower liver function, inflammation of your liver, jaundice (yellowing of the skin or eyes), higher levels of bilirubin (measured in a blood test), erythema multiforme (red spots of different shapes on the skin), Stevens-Johnson syndrome (a serious skin condition where you have reddening and scaling of your skin, blistering or raw sores, or detachment of the top layer of skin from bottom layers), lower amount of urine produced, enlargement of the mammary glands in males.

Very Rare(affects less than 1 in 10,000 people)

Swelling in your intestine (intestinal angioedema).

**Lercanidipine**

Rare(affects less than 1 in 1,000 people)

Angina pectoris (chest pain due to lack of blood to your heart), vomiting, heartburn, muscle pain.

Very Rare(affects less than 1 in 10,000 people)

Chest pain.

Patients with pre‑existing angina pectoris may experience increased frequency, duration or severity of the attacks with the group of medicines to which lercanidipine belongs. Isolated cases of heart attack may be observed.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. You can ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V\*. By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Coripren**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture. Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**6. Contents of the pack and other information**

**What Coripren contains**

The active substances are enalapril maleate and lercanidipine hydrochloride.

Each film-coated tablet contains: 20 mg enalapril maleate (equivalent to 15.29 mg enalapril) and 20 mg lercanidipine hydrochloride (equivalent to 18.88 mg lercanidipine).

The other ingredients are:

Core: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone K30, sodium hydrogen carbonate, magnesium stearate.

Film-coating: hypromellose, titanium dioxide (E171), macrogol 6000, Iron oxide yellow (E172), talc, Iron oxide red (E172).

**What Coripren looks like and contents of the pack**

Coripren 20 mg/20 mg tablets are orange, circular and biconvex tablets of 11 mm.

Coripren 20 mg/20 mg is available in packs of 7, 14, 28, 30, 35, 42, 50, 56, 90, 98 and 100 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorization Holder:

RECORDATI Industria Chimica e Farmaceutica S.p.A. – Via Matteo Civitali 1 – 20148 Milan, Italy

Manufacturer:

RECORDATI Industria Chimica e Farmaceutica S.p.A. – Via Matteo Civitali 1 – 20148 Milan, Italy

**This medicinal product is authorised in the Member States of the EEA under the following names:**

Coripren Italy

Coripren Spain

**This leaflet was last approved in (MM/YYYY)**

Module 4

Labelling

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Coripren 20 mg/20 mg film-coated tablets

enalapril maleate/lercanidipine hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains: 20 mg enalapril maleate (equivalent to 15.29 mg enalapril) and 20 mg lercanidipine hydrochloride (equivalent to 18.88 mg lercanidipine).

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

7 film-coated tablets

14 film-coated tablets

28 film-coated tablets

30 film-coated tablets

35 film-coated tablets

42 film-coated tablets

50 film-coated tablets

56 film-coated tablets

90 film-coated tablets

98 film-coated tablets

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP: MM/YYYY

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from light and moisture.

Do not store above 25°C

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

**Marketing Authorisation Holder**

RECORDATI Industria Chimica e Farmaceutica S.p.A.

Via Matteo Civitali 1

I-20148 Milan

Italy

**12. MARKETING AUTHORISATION NUMBER(S)**

MA number:

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Coripren 20mg/20mg

|  |
| --- |
| **MINIMUM PARTICULARS TO APPEAR ON BLISTERS**  **Polyamide-aluminium-PVC/aluminium BLISTERS** |

|  |
| --- |
| **1. NAME OF THE MEDICINAL PRODUCT** |

Coripren 20 mg/20 mg tablets

enalapril maleate/lercanidipine hydrochloride

|  |
| --- |
| **2. NAME OF THE MARKETING AUTHORISATION HOLDER** |

RECORDATI Industria Chimica e Farmaceutica S.p.A.

|  |
| --- |
| **3. EXPIRY DATE** |

EXP: MM/YYYY

|  |
| --- |
| **4. BATCH NUMBER** |

Batch

|  |
| --- |
| **5. OTHER** |

Module 5

Scientific discussion during the initial procedure

1. Introduction

Based on the review of the data and the Applicant’s response to the questions raised by RMS and CMS on quality, safety and efficacy, the RMS considers that the application for CORIPREN in the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled with enalapril 20 mg and lercanidipine 20 mg and given concurrently as separate tablets, is approvable.

This is a decentralised application for a line extension for a new strength of the FDC of enalapril and lercanidipine of 20 mg each (dose combinations of 10 or 20 mg Enalapril together with 10 mg Lercanidipine have already been registered).

CORIPREN is a medicine consisting of a combination of two active substances: enalapril and lercanidipine (ATC code: C09BB02).

Enalapril is a pro-drug that is hydrolyzed by esterases in the liver to produce the active angiotensin-converting enzyme (ACE) inhibitor Enalaprilat . Lercanidipine is a Calcium channel blocker acting on L-type channels located in vascular smooth muscles which leads to vaodilation and blood pressure reduction. Both drugs induce vasodilation via different mechanisms: Enalaprilat reduces the vasoconstrictive effect of angiotensin II and augments the vasodilation induced by bradykinin (which is degraded by ACE), whereas Lercanidipine acts via decreasing the intracellular Ca concentration in vascular smooth muscle cells. The therapeutic sense of the combination is explained by the Enalapril-induced antagonism of the stimulation of the renin-angiotensin-aldosterone system and of the sympathetic nervous system by Lercanidipine.

To support the **line extension** application the following clinical studies were submitted:

* a pivotal bioequivalence study, to demonstrate the bioequivalence of lercanidipine (20 mg) and enalapril (20 mg) administered in single dose concomitantly as a FDC or as a free combination of marketed tablets in healthy male and female subjects (IT-PK-0394)
* an interaction study, to investigate the pharmacokinetics of lercanidipine 20mg and enalapril 20mg administered as mono-components and as a free combination in order to assess the effect of lercanidipine on enalapril pharmacokinetic parameters and vice versa following single oral administration of the two drugs in healthy male and female volunteers (IT-PK-0337)
* a double-blind, randomized factorial study assessing the effects of lercanidipine (10 and 20 mg) and of enalapril (10 and 20 mg) *vs.* placebo and the four combinations of the two drugs, to provide adequate proof that each substance makes a contribution to the antihypertensive effect of the combination 20mg/20mg, and that with the use of lercanidipine and enalapril in combination there is an increase of the therapeutic activity and an improvement in tolerability because of the counteracting by one substance of the adverse reactions produced by the other (IT–CL-0336).

A bioequivalence study initially performed with a different formulation (IT-PK-0354) and a pilot bioequivalence study testing two different formulations (IT-PK-0377) were also included in the dossier for completeness and for the evaluation of safety.

.

Compliance to GCP was stated.

The Reference Member States (RMS) has been assumed that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of competent manufacturer authorization issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Dr. Lino Pontello, graduated in pharmaceutical chemistry and technology, Milan, Italy is the quality expert and acts as QP at Recordati, Milan, Italy.

A declaration by the QP at the site responsible for batch release that the active substances are manufactured in accordance with the detailed guidelines on GMP for starting materials was submitted.

Since an old inspection for Dr. Reddy’s Laboratories Plot 116, responsible for enalapril maleate production, was reported, a declaration by Dr. Reddy’s was released, according to the enalapril maleate is currently manufactured and will be supplied by Peddadevulapally Unit V, which inspection was conducted by Recordati in 2012.

1. About the product

|  |  |
| --- | --- |
| **Proposed name of the medicinal product in the RMS** | **CORIPREN 20mg/20mg compresse rivestite con film** |
| **Name of the drug substances (INN name):** | enalapril maleate, lercanidipine hydrochloride |
| **Pharmaco-therapeutic group (ATC Code):** | Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers: enalapril and lercanidipine.  ATC code: C09BB02 |
| **Pharmaceutical form(s) and strength(s):** | Film Coated Tablet  20 mg/ 20 mg |
| **Reference Number(s) for the Decentralised Procedure** | IT/H/0266/003/DC |
| **Reference Member State:** | IT |
| **Concerned Member States:** | ES |
| **Marketing Authorisation Numbers** | AIC No: |
| **Name and address of the Authorization Holder** | RECORDATI Industria Chimica e Farmaceutica S.p.A. – Via Matteo Civitali 1, I-20148 Milan, Italy |

1. Scientific Overview and discussion

III.1 Quality aspects

ACTIVE SUBSTANCE – ENALAPRIL MALEATE

INN: Enalapril maleate

Chemical Name: (2*S*)-1-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid (*Z*)-butenedioate.

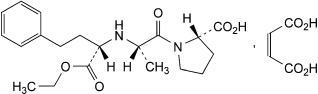
Molecular Formula: C24H32N2O9

CAS number: 76095-16-4

The **Enalapril maleate** drug substance is a white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

The chemistry manufacturing and controls information for the description of manufacturing process and process control of enalapril maleate drug substance has been evaluated by the European Directorate for the Quality of Medicines (EDQM) for the grant of the European Certificate of Suitability.

Structure:



Molecular weight: 492.5 g/mol

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

ACTIVE SUBSTANCE: LERCANIDIPINE HYDROCHLORIDE

INN: Lercanidipine hydrochloride

Chemical Name:

2-[(3,3-Diphenylpropyl)methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-

2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

1,1-Dimethyl-2-[N-(3,3-diphenylpropyl)-N-methylamino]ethyl methyl 2,6-

dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

hydrochloride.

1,1-Dimethyl-2-[N-(3,3-diphenylpropyl)-N-methylamino]ethyl 2,6-dimethyl-

5-metho-xycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate

hydrochloride.

1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-

[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester

hydrochloride.

3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-

[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester

hydrochloride (CA).

Molecular Formula: C36H41N3O6 · HCl

CAS number for lercanidipine hydrochloride base and salt are: [132866-11-6] and [100427-26-7] respectively.

Structure:



Lercanidipine HCl exhibits chirality because of an asymmetric centre at position 4 of the 1,4-dihydropyridine ring.

Molecular weight: 648.205 g/mol

The active substance Lercanidipine hydrochloride was developed by Recordati Industria and is not included in any Pharmacopoeia.

Solubility: Sparingly soluble in water, very soluble in dimethylformamide, dimethylsulphoxide, chloroform and acetic acid.

melting point: the melting temperature range for lercanidipine hydrochloride polymorph form I, the required polymorphic form, is 185-190°C.

Hygroscopicity: Lercanidipine HCl is not hygroscopic, at 60-70% relative humidity, the material absorbed no more than 0.8% water.

Dissociation Constant: the pKa' value is 7.2 at 37°C.

Partition coefficient: log P is 6.47.

Polymorphism: Lercanidipine exists in two polymorphic forms I and II which can be differentiated by DSC, FT/IR and X-Ray diffraction. Polymorph form I is used for the manufacture of the Lercanidipine HCl tablets. The Lercanidipine HCl is controlled to not more than 3.0% form II (limit for form II in the drug substance specification: NMT 1.0 %).

All aspects of the manufacture and control of the active substance Lercanidipine hydrochloride, including the proposed packaging specifications and appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**DRUG PRODUCT**

The applied product 20 mg/20 mg tablets were developed as immediate release tablets for oral administration containing 20 mg Lercanidipine HCl and 20 mg Enalapril maleate.

The tablets are intended for a reduction of blood pressure, when the essential hypertension is not adequately controlled by monotherapy.

The medicinal product is presented as orange, circular shaped, biconvex.

All the excipients of the core tablet also comply with the requirements of the relevant Ph.Eur. monographs and are all well established and are commonly used in pharmaceutical products of this type.

**Other Ingredients**

Tablet Core:

Lactose monohydrate, cellulose microcrystalline, sodium starch glycollate, povidone, sodium hydrogen carbonate, magnesium stearate, purified water\*.

\*removed during processing.

Film coating:

Opadry 02F23516, corresponding to : hypromellose 5 cP, titanium dioxide, macrogol 6000, talc, iron oxide yellow, iron oxide red and purified water\*.

\*removed during processing.

All the excipients comply with their respective European Pharmacopeia monographs, with the exception of iron oxide yellow and iron oxide red, described and compliant with USP/NF.

The qualitative formulation was developed and each of the excipients was selected for its intended use based on optimization studies. They are included in the formulation at suitable levels and for recognized purposes.

Magnesium stearate is of vegetable origin.

There are no excipients of human or animal origin except lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The formulation of E20/L20 film-coated tablets has been developed based on the formulation of the already authorized fixed combination Enalapril maleate 10 mg/Lercanidipine hydrochloride 10 mg (E10/L10) film-coated tablets. The composition of the tablet core of the new strength is quantitatively proportional to that of the authorized E10/L10 strength.

Suitable pharmaceutical development data has been provided for this application.

The clinical development of the combination of Enalapril maleate 20 mg/ Lercanidipine hydrochloride 20 mg has been performed using the marketed monotherapy products in various strengths and combinations, rather than the fixed combination product.

Bioequivalence of the E20/L20 fixed combination film-coated tablets vs. the free combination of the single marketed products, Lercanidipine hydrochloride 20 mg tablets (Lerdip® 20 mg) and Enalapril maleate 20 mg tablets (Xanef® 20 mg), has been demonstrated.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been adequately validated.

**Control of Finished Product**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided the working standard used.

**Container Closure System**

The container closure system consists of a blister obtained starting from a polyamide/aluminium/ polyvinylchloride film (PA/Al/PVC), which is heat-sealed to an aluminium foil.

Stability studies were performed to demonstrate that the container system is physically and chemically compatible with the product, even in stressed conditions.

Pack sizes: 7, 14, 28, 30, 35, 42, 50, 56, 90, 98 and 100 tablets .

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

**Stability**

Finished product stability studies were performed according to the current ICH stability guideline guidelines on batches of finished product packed in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been justified, when the product is stored in the original package, in order to protect it from light and moisture and at temperature not above 25°C.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological profiles of Enalapril + Lercanidipine are well known. As Enalapril and Lercanidipine are two widely used, well-known active substances, no additional studies are provided and further studies are not required. Overview based on literature review is deemed appropriate.

Since this is a line extension for a new strength, the Applicant refers to the previously submitted Non-clinical Overview dated December 2004.

Since this FDC is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

The clinical development program to support the line extension for the additional strength 20mg/20mg includes:

* a pivotal bioequivalence study, to demonstrate the bioequivalence of lercanidipine (20 mg) and enalapril (20 mg) administered in single dose concomitantly as a FDC or as a free combination of marketed tablets in healthy male and female subjects (IT-PK-0394)
* an interaction study, to investigate the pharmacokinetics of lercanidipine 20mg and enalapril 20mg administered as monocomponents and as a free combination in order to assess the effect of lercanidipine on enalapril pharmacokinetic parameters and vice versa following single oral administration of the two drugs in healthy male and female volunteers (IT-PK-0337)
* a double-blind, randomized factorial study assessing the effects of lercanidipine (10 and 20 mg) and enalapril (10 and 20 mg) *vs.* placebo and the four combinations of the two drugs, to provide adequate proof that each substance makes a contribution to the antihypertensive effect of the combination 20mg/20mg, and that the use of lercanidipine and enalapril in combination provides an increase of the therapeutic activity and an improvement in tolerability because of the counteracting effect of one substance to the adverse reactions produced by the other (IT–CL-0336).

**Pharmacokinetics**

Bioequivalence has been demonstrated for the FDC applied for and the reference mono-products. It is demonstrated the absence of a relevant interaction between 20 mg enalapril and 20 mg lercanidipine.

**EFFICACY**

Taking into account that this application is a line extension of approved strengths and that this FDC is proposed “*as substitution therapy in adult patients whose blood pressure is adequately controlled with enalapril 20 mg lercanidipine 20 mg and given concurrently as separate tablets*“, efficacy data provided are deemed adequate.

**SAFETY**

According to the indication proposed, this FDC will be prescribed to those patients who are already successfully treated with enalapril 20mg/lercanidipine 20mg as free combinations, thus excluding the population who are at higher risk of therapy failure or toxicity with ACE-Is and/or CCBs.

Moreover, the SmPC sections have been amended according to the recommendations recently made by the Agency’s Pharmacovigilance Risk Assessment Committee (PRAC).

**PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN**

A summary of Pharmacovigilance System has been presented. It, as decsribed by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable EU-Risk Management plan has been provided for this product.

The explanation of the important identified risks and the labelling of the risks in the SPC are considered appropriate. The RMP submitted has been approved.

**SUMMARY OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING**

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPC sections have been amended according to the recommendations made by the Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) in April 2014 and then endorsed by CHMP (EMA/294911/2014 (23 May 2014). The review of RAS-acting agents was initiated at the request of the Italian Medicines Agency (AIFA), under Article 31 of Directive 2001/83/EC.

The PIL is consistent with the details in the SmPC and both are in-line with the current guidelines. The labelling is in-line with current guidance.

IV Overall conclusions and benefit-risk assessment

The quality characteristics of **Coripren 20 mg/20 mg film coated tablets** are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch.

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of enalapril maleate and lercanidipine hydrochloride are well-known, no additional data were required.

From the non-clinical point of view no safety concerns have been identified

The SmPC, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines. Moreover, the SmPC sections have been amended according to the recommendations made by the Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) in April 2014 and then endorsed by CHMP (EMA/294911/2014 (23 May 2014).

**BENEFITI RISK ASSESSMENT**

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Three post approval commitments related to quality aspects have been agreed.

Bioequivalence with the reference mono-products has been demonstrated and no relevant interaction between 20 mg enalapril and 20 mg lercanidipine has been shown.

An adequate review of published clinical data has been provided and the issues raised during preliminary assessment have been solved.

Then, clinical efficacy and safety of the FDC can be assumed, taking into account that this is a line extension of approved strengths and that this FDC is proposed “*as substitution therapy in adult patients whose blood pressure is adequately controlled with enalapril 20 mg lercanidipine 20 mg and given concurrently as separate tablets*“.

The benefit/risk balance is, therefore, considered to be positive.