National Institute of Pharmacy
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Budapest, Hungary

GYEMSZI
Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet

Public Assessment Report

Name of the Product:

Elernap

10 mg/10 mg and 20 mg/10 mg film-coated tablets

(enalapril maleate/lercanidipine)

Procedure number:

HU/H/0334/001-002/DC

Marketing authorisation holder: Krka d.d.

Date: 30 December 2013

CONTENT

LAY SUMMARY

After careful assessment of their quality and therapeutic benefit/risk ratios, the member states authorised for marketing the fixed combinations of enalapril (as maleate)/lercanidipine (as hydrochloride salt) 10 mg/10 mg and 20 mg/10 mg under the name of Elernap (in Austria Enalapril/Lercanidipine Krka, in Bulgaria and Czech Republic Lenop, in Lithuania Elymo) film-coated tablets. The holder of the marketing authorisation is Krka, d.d., Novo mesto, Slovenia.

Each film-coated tablet contains 10 or 20 mg enalapril maleate (equivalent to 7.64 mg or 15.29 mg enalapril, respectively) and 10 mg lercanidipine hydrochloride (equivalent to 9.44 mg lercanidipine).

The other ingredients are:
- tablet core: povidone K30, maleic acid, sodium starch glycolate type A, lactose monohydrate and sodium stearyl fumarate,
- film coating: hypromellose, titanium dioxide (E171), talc, macrogol 6000.
  Moreover, the 20 mg/10 mg strength contains also yellow iron oxide (E172) and quinoline yellow (E104).

Appearance:
- the 10 mg/10 mg strength is white, round, slightly biconvex film-coated tablet with bevelled edges,
- the 20 mg/10 mg strength is yellow, round, slightly biconvex film-coated tabletwith bevelled edge.

The Elernap film-coated tablets are available in blister packs in cartons.

Elernap film-coated tablets represent is a fixed combination of an ACE-inhibitor (enalapril) and a calcium channel blocker (lercanidipine), two medicines that lower blood pressure. They are used for the treatment of high blood pressure (hypertension) in patients whose blood pressure is not adequately controlled by enalapril 10 mg or 20 mg alone. Elernap film-coated tablets should not be used for initial treatment of hypertension.

What should be known before taking Elernap film-coated tablets

Do not take Elernap film-coated tablets who
- are allergic to enalapril or lercanidipine or any of the other ingredients of this medicine;
- are allergic to medicines closely related to Elernap film-coated tablets (e.g. amlodipine, felodipine, nifedipine, captopril, fosinopril, lisinopril, ramipril);
- are more than 3 months pregnant. (It is also better to avoid taking Elernap film-coated tablets in early pregnancy – see pregnancy section);
- suffer from certain heart diseases:
  - untreated congestive heart failure,

  - obstruction to the flow of blood from the left ventricle of the heart, including a narrowing of the aorta (aortic stenosis),
  - unstable angina pectoris (angina at rest or progressively increasing angina),
  - within one month after suffering a heart attack (myocardial infarction);
- have severe liver or kidney problems, or if you are undergoing dialysis;
- use medicines such as:
  - antifungals (e.g. ketoconazole, itraconazole),
  - macrolide antibiotics (e.g. erythromycin, troleandomycin),
  - antivirals (e.g. ritonavir);
- are simultaneously using a medicine known as ciclosporin;
- together with grapefruit or grapefruit juice;
- have ever developed angioedema (oedema of the face, lips, tongue, and/or larynx, hands, and feet), either hereditary in type or after previous treatment with an ACE-inhibitor;
- have a hereditary tendency to tissue swelling or if you develop tissue swelling of unknown cause (hereditary or idiopathic angioedema).

Warnings and precautions

Inform their doctor before taking Elernap film-coated tablets who:
- suffer from heart disease involving interruption of blood flow (ischaemia);
- suffer from a disturbance of blood flow in the brain (cerebrovascular disease);
- have any of the following heart diseases: heart failure, narrowing (stenosis) of the opening of the aortic or mitral valve or enlarged heart (hypertrophic cardiomyopathy);
- have renal problems (mild to moderate renal impairment);
- have liver enzyme levels risen or developed jaundice;
- have reduced white blood cells to various degrees (leucopenia, agranulocytosis), possibly resulting in susceptibility to infection and severe general symptoms;
- suffer from certain diseases of the connective tissue with involvement of blood vessels (collagen vascular diseases);
- are simultaneously taking allopurinol (an anti-gout medicine), procainamide (a medicine used to combat irregular heartbeat), or lithium (a medicine used to combat certain types of depression);
- develop hypersensitivity reactions or tissue swelling (angioedema) during treatment with Elernap film-coated tablets;
- suffer from diabetes mellitus;
- develop a persistent dry cough;
- are at risk of an elevation of the potassium level in your blood. This may occur in following conditions for example: impaired renal function, age over 70 years, treatment with potassium-sparing diuretics. As blood potassium levels can be detected by laboratory tests, the doctor's instructions should be followed;
- have an inadequate reduction in blood pressure because of the ethnic origin (especially in patients with black skin);
- think they are (or might become) pregnant. Elernap film-coated tablets are is not recommended in early pregnancy, and must not be taken by women who are more than 3 months

pregnant, as it may cause serious harm to the baby if used at that stage (see pregnancy section).

For those who require desensitisation therapy for insect venom (e.g. from bees or wasps), Elernap film-coated tablets should be temporarily replaced by a suitable medicine of a different type. Otherwise, life-threatening general symptoms may occur. Such reactions can also occur after insect bites (e.g. bee or wasp stings).

Use of Elernap film-coated tablets while receiving dialysis or treatment for greatly elevated blood lipid levels can result in severe hypersensitivity reactions and even life-threatening shock. Those who require dialysis and prescribed Elernap film-coated tablets should inform the doctor, for the doctor can take this into account when prescribing the adequate treatment.

Those who are shortly to undergo an operation or anaesthesia (including dental anaesthesia), inform their doctor that they are taking Elernap film-coated tablets, since an abrupt fall in blood pressure could occur during anaesthesia.

Use of this medicine requires regular medical monitoring. Therefore, patients should be absolutely sure to undergo whatever laboratory tests and examinations your doctor orders.

Children and adolescents

The safety and efficacy of Elernap film-coated tablets has not been demonstrated in controlled studies in children.

Other medicines and Elernap film-coated tablets

Consult their doctor who are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. When Elernap film-coated tablets is taken simultaneously with certain other medicines, the effect of Elernap film-coated tablets or of the other medicine may be intensified or weakened, or certain side effects may occur more frequently.

The blood pressure-lowering effect can be intensified when using any of the following medicines together with Elernap film-coated tablets:
- ciclosporin (a medicine that suppresses the immune system);
- oral antifungal medicines such as ketoconazole and itraconazole;
- antiviral agents such as ritonavir;
- macrolide antibiotics such as erythromycin or troleandomycin;
- the anti-ulcer medicine cimetidine at daily doses of more than 800 mg;
- diuretics such as hydrochlorothiazide, chlorthalidone, furosemide, triamterene, amiloride, indapamide, spironolactone, or other blood pressure-lowering medicines;
- certain vasodilatating agents such as glyceryl trinitrate and organic nitrates (isosorbide) or anaesthetic agents;
- certain antidepressant and antipsychotic medicines;
- baclofene.

The blood pressure-lowering effect can be weakened if using any of the following medicines together with Elernap film-coated tablets:
- certain painkillers (e.g. paracetamol, ibuprofen, naproxen, indomethacin, or aspirin unless used at low dosage);
- medicines acting on blood vessels (e.g. noradrenaline, isoprenaline, dopamine, salbutamol);
- anticonvulsants such as phenytoin and carbamazepine;
- rifampicin (a drug for the treatment of tuberculosis).

Those who use digoxin (a medicine that influences the tone of the heart muscle) ask their doctor what signs you should look out for.

Those who use potassium-sparing diuretics (spironolactone) or potassium supplements, the level of potassium in your blood may increase.

Simultaneous use of lithium carbonate and Elernap film-coated tablets can lead to lithium toxicity.

Those who use immunosuppressant or anti-gout medicines may in very rare cases be susceptible to severe infections.

Those who suffer from diabetes note that simultaneous use of Elernap film-coated tablets and either insulin or oral antidiabetic agents such as sulfonylureas and biguanides can result in hypoglycaemia (excessive reduction of blood sugar level) during the first month of treatment.

Those who are using antihistamines such as terfenadine or astemizole or anti-arrhythmic agents such as amiodarone or quinidine, or estramustine or amifostine or gold, consult their doctor since certain drug interactions can occur with these agents.

Elernap film-coated tablets with food and alcohol

This medicine should be taken at least 15 minutes before a meal.

Alcohol can increase the effect of Elernap film-coated tablets. Patients are therefore advised either to consume no alcohol or, at least to strictly limit their alcohol intake.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, consult their doctor before taking this medicine. The doctor will normally advise to stop taking Elernap film-coated tablets before the patient would become pregnant or as soon as they realise they became pregnant and will advise to take another medicine. Elernap film,-coated tablets is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to the baby if used after the third month of pregnancy.

Those who are breast-feeding or about to start breast-feeding also consult their doctor. Breast-feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking Elernap film-coated tablets. In the case of an older baby the doctor should advise you on the benefits and risks of taking Elernap film-coated tablets whilst breast-feeding, compared with other treatments.

Driving and using machines

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

Elernap film-coated tablets contain lactose

Those who have been informed by their doctor that they have intolerance to lactose (milk sugar), contact their doctor before taking this medicinal product.

How to take Elernap film-coated tablets

Unless otherwise prescribed by the doctor, the usual dose is one film-coated 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.

The tablets should not be taken with grapefruit or grapefruit juice.

What to do when more Elernap film-coated tablets were taken than prescribed

If the patient has taken more than the dose prescribed by your doctor or in the event of overdosage, seek medical attention immediately and if possible take the tablets and/or the container with you to the doctor.

Taking more than the correct dose can cause your blood pressure to fall too far and your heart to beat irregularly or faster. This can result in loss of consciousness.

In addition, a severe fall in blood pressure can result in reduced blood flow to important organs, cardiovascular failure, and renal failure.

What to do if taking Elernap film-coated tablets was forgotten

If the patient forgets to take the tablet, take the missed tablet as soon as possible unless it is almost time for the next dose. Then continue taking the tablets as usual. Do not take a double dose to make up for a forgotten dose.

Stopping taking Elernap film-coated tablets

If the patient stops taking Elernap film-coated tablets, his/her blood pressure may rise again. Thus, patients need to consult their doctor before stopping taking Elernap film-coated tablets.

Possible side effects

Like all medicines, Elernap film-coated tablets can cause side effects, although not everybody experiences them.

Those who develop any of the following signs or symptoms should inform their doctor immediately:
- swelling of the face, limbs, lips, mucous membranes, tongue, and/or larynx, or shortness of breath;
- yellow colouration of the skin and mucous membranes;
- fever, swelling of the lymph nodes, and/or inflammation of the throat.

In such cases you must stop taking <Invented name> and your doctor will take appropriate measures.

The most frequent side effects (1 to 10% frequency) observed with Elernap film-coated tablets are cough, headache, dizziness, peripheral oedema and rash.

All adverse effects observed either with Elernap film-coated tablets or with enalapril or lercanidipine alone are listed below.

Very common (may affect more than 1 in 10 people):
- blurred vision,
- dizziness,
- cough,
- nausea,
- feeling of weakness.

Common (may affect up to 1 in 10 people):
- headache, depression,
- swelling of the ankles, excessive reduction in blood pressure including excessive fall in blood pressure when standing up, brief loss of consciousness (fainting), heart attack or stroke, chest pain, a feeling of tightness in the chest, abnormal heart rhythm, increased heart rate,
- shortness of breath,
- diarrhoea, abdominal pain, altered taste,
- flushing of the face, reddening and warm sensation in the skin, skin rashes, swelling of the face, lips, tongue, throat, hands,

- tiredness, facial reddening,
- increased potassium level in blood, increased creatinine level in blood.

Uncommon (may affect up to 1 in 100 people):
- anaemia,
- excessively low blood sugar levels,
- confusion, drowsiness, sleeplessness, nervousness, abnormal sensations (e.g. pins and needles),
- heart pounding,
- nasal discharge, sore throat and hoarseness, wheezing, asthma,
- intestinal obstruction, inflammation of the pancreas, vomiting, digestive disturbances, constipation, loss of appetite, gastric irritation, mouth dryness, gastric ulcer,
- increased sweating, itch, nettle rash, hair loss,
- kidney problems,
- impotence,
- muscle cramps, ringing in the ears, malaise, fever,
- increased urea level in blood, reduced sodium level in blood.

Rare (may affect up to 1 in 1,000 people):
- reduction in the number of certain blood cells, reduction in certain laboratory values (haemoglobin and haematocrit), reduced bone marrow function, lymph node swelling, autoimmune diseases,
- altered dreams, sleep disturbances,
- coldness of the hands and feet,
- abnormalities in the lung tissue, sniffling, inflammation of the lung,
- inflammation and ulceration of the mucous membrane of the mouth, inflammation of the tongue,
- liver failure, inflammation of the liver, jaundice (yellowing of the skin and/or the whites of the eyes),
- severe skin reactions. A symptom complex has been described that can be associated with some or all of the following side effects: fever, inflammation of serous surfaces, inflammation of blood vessels, muscle and joint pain / muscle and joint inflammation and certain changes in laboratory values; skin rash, light sensitivity and other skin reactions can occur,
- reduced urine output, increased urine output,
- breast enlargement in men,
- increased laboratory values (liver enzymes, serum bilirubin).

Very rare (may affect up to 1 in 10,000 people): gum thickening, intestinal swelling.

Not known (frequency cannot be estimated from the available data): syndrome of inappropriate antidiuretic hormone secretion (SIADH)

How to store Elernap film-coated tablets<Invented name>

Store it in the original package in order to protect from moisture.

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

Scientific discussion

during the initial procedure

This module reflects the scientific discussion for the approval of Elernap 10 mg/10 mg and 20 mg/10 mg film-coated tablets. The procedure was finalised at 28 June 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the member states concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Austria, Bulgaria, Czech Republic, Estonia, Finland, Ireland, Latvia, Lithuania, Poland, Portugal, Slovakia, Slovenia and Spain) concerned the generic version of a fix combination of enalapril/lercanidipine 10 mg/10 mg and 20 mg/10 mg.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new non-clinical or clinical data, other than supporting literature where necessary and a bioequivalence study.

Enalapril/lercanidipine combination has a dual mechanism of action; the ACE inhibiting action of enalapril and the calcium channel antagonist lercanidipine. The enalapril component Enalapril/Lercanidipine combination inhibit the angiotensin converting enzyme which catalyses the conversion of angiotensin I to the vasopressor agent angiotensin II. Since ACE is identical to kininase II, enalapril may also inhibit the degradation of bradykinin, a potent vasodepressor peptide. The lercanidipine component of these Medicinal Products is a calcium antagonist of the dihydropyridine group; it 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. Due to its high membrane partition coefficient, lercanidipine has a prolonged antihypertensive action, and is devoid of negative inotropic effects because of its high vascular selectivity.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Elernap (in Austria: Enalapril/Lerconidipine Krka, in Portugal Lenap, in Lithuania and Slovenia Elyrno) 10 mg/10 mg and 20 mg/10 mg film-coated tablets from Krka d.d., Novo mesto, Slovenia.

Elernap 10 mg/10 mg and 20 mg/10 ml film-coated tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by lercanidipine 10 or 20 mg alone.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Elernap 10/10 mg and 20/10 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Krka.

The reference products are Zaneril® 10 mg/10 mg and Zaneril® 20 mg/10 mg film-coated tablets (containing 10 mg or 20 mg enalapril maleate and 10 mg lercanidipine hydrochloride as active ingredients) which were the original products of Recordati Industria Chimica e Farmaceutica S.p.A. Carmen® ACE film-coated tablets (Recordati, EU) used in the bioequivalence study are the same products, marketed under different name.

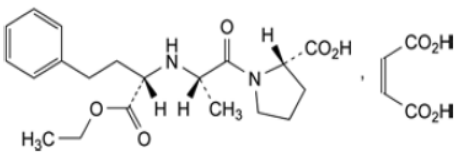
II.2 Drug Substances

II.2.1 Enalapril maleate

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The CEP indicates that the Ph. Eur. monograph is suitable to control the purity of the substance.

The Quality Overall Summary is adequate.

INN name: enalapril maleate
Chemical name: (2*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]-amino]propanoyl]pyrrolidine-2-carboxylic acid (*Z*)-butenedioate
Structure:



The 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.

Enalapril maleate is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents and residual catalyst.

The Ph. Eur. specification includes the following tests: characters, identification by IR, appearance of solution, pH, specific optical rotation, heavy metals, related substances, loss on drying, sulphated ash and assay.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Conference on Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period of 48 months and the packaging material (polyethylene bag inside an aluminium bag, placed in a fibre drum) have been mentioned in the CEP.

Good Manufacturing Practice (GMP) compliance of the active substance manufacture is demonstrated by the applicant.

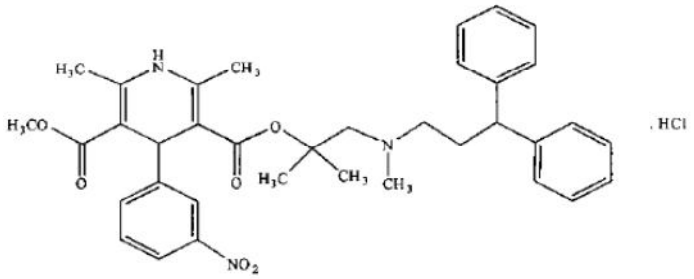
II.2.2 Lercanidipine Hydrochloride

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier.

The Quality Overall Summary is adequate.

INN name: lercanidipine hydrochloride
Chemical name: 1,4-dihydro-2,6-dimethyl-4-(3 -nitrophenyl)-3,5-pyridinedicarboxylic acid-2-[(3,3 -diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester hydrochloride

Structure:



The active substance is a yellow powder, soluble in methanol, practically insoluble in water. Lercanidipine hydrochloride has one chiral centre. It exhibits two isomers i.e. (S)-lercanidipine and (R)-lercanidipine hydrochloride and it shows polymorphism. The manufacturer consistently produces the racemate and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the substance provided is adequate.

Evidence of the structure has been confirmed by IR spectroscopy, UV spectroscopy, MS, ^{1}H-NMR and X-ray diffraction. Batch-to-batch consistency of the polymorphic form is routinely tested by X-ray diffraction. The impurity profile of the active substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Lercanidipine hydrochloride is not official in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: description, data on solubility, identification by IR, HPLC, X-ray, DSC and reaction of chlorides, loss on drying, melting range, specific optical rotation, sulphated ash, heavy metals, related substances, residual solvents, assay, particle size distribution and microbiological purity.

The specification is in accordance with the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Test methods are adequately described and sufficiently validated. Reference materials used by the active substance manufacturers and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data a retest periods of 48 months packed under nitrogen atmosphere in clear polythene bag followed by triple laminated aluminium bag in HDPE drum, stored below 25 ºC in an airtight container, protected from light, is acceptable.

Good Manufacturing Practice (GMP) compliance of the active substance manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The objective of the pharmaceutical development was to develop a stable tablet dosage form of combination of enalapril maleate and lercanidipine hydrochloride, the generic equivalent to Carmen ACE® film coated tablets, the innovator product of Recordati.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the products are shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies the following appearance, composition and packaging was obtained.

- Elernap 10/10 mg film-coated tablets: white, round, slightly biconvex film-coated tablets with bevelled edges.
- Elernap 20/10 mg film-coated tablets: yellow, round, slightly biconvex film-coated tablets with bevelled edges

The tablets are packed in OPA/Al/PVC//Al blisters and cardboard box.

The excipients used in the finished product are povidone K30, maleic acid, sodium starch glycolate type A, lactose monohydrate, sodium stearyl fumarate, Opadry white and yellow (which contains hypromellose, yellow iron oxide (E172), titanium dioxide (E171), talc, Quinoline yellow (E104) and macrogol). All excipients used comply with their respective Ph. Eur. monograph, with exception of Opadry film coating agents. However, their components also comply with its requirements. Compliance of the products with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method have been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form

monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was established. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented. Certificates of analysis were also provided for the enalapril maleate and lercanidipine hydrochloride working standards and of the impurity reference standards.

The container closure system of the product is OPA/Al/PVC//Al blister and cardboard box. Specification and analytical test methods are described. IR spectra and certificates of analysis justifying the conformity to the Ph. Eur. monograph 3.1.11. and relevant EC Directives are provided.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with storage condition of "store in the original packaging in order to protecting from moisture" is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substances and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This abridged application refers to the dossier of a reference product (generic submission). Thus, no new non-clinical data are normally required.

The pharmaco-toxicological properties of both enalapril and lercanidipine are well-known. The non clinical overview is therefore based on a review of data available in several scientific databases or published in relation to enalapril and lercanidipine given either alone or in combination.

III.2 Pharmacology

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acids, 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.

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. Due to its high membrane partition coefficient, lercanidipine has a prolonged antihypertensive action, and is devoid of negative inotropic effects because of 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.

No specific new non-clinical studies have been performed, which is acceptable for this type of application.

III.3 Pharmacokinetics

Enalapril

Oral enalapril is rapidly absorbed. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is high. The absorption of oral enalapril is not affected by the presence of food in the gastrointestinal tract.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor.

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

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat and unchanged enalapril (about 20%).

Lercanidipine

Lercanidipine is completely absorbed after oral administration.

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 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 low.

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

The degree of plasma protein binding of lercanidipine is high.

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.

Elimination essentially occurs through biotransformation.

No specific new non-clinical studies have been performed, which is acceptable for this type of application.

III.4 Toxicology

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

No new toxicological studies have been performed, which is acceptable for this type of application.

III.5 Ecotoxicity/environmental risk assessment

Since Elernap film-coated tablets are intended to substitute other similar products on the market, its storage, distribution, use and disposal will not result in an increase of risk to the environment. No environmental risk assessment is therefore deemed necessary.

III.6 Discussion on the non-clinical aspects

As the pharmacodynamic, pharmacokinetic and toxicological properties of both enalapril and lercanidipine are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical overview has been written by an appropriately qualified expert and is satisfactory, providing and appropriate review of the pharmacology, and toxicology of the products.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of the products from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Except for establishing bioequivalence to the reference product, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

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

Human pharmacokinetic data of the individual components are summarised below.

Enalapril

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.

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%.

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

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%).

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 dialysis clearance is 62 ml/min.

After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7 µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7 µg/L (range 1.2 to 2.3 µg/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 1.44 µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2 µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

Lercanidipine

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 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.

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.

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 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.

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.

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.

IV.2.2 Bioequivalence study

To support the application, the applicant submitted one bioequivalence study report. The bioequivalence study was carried out with the highest strength (enalapril/lercanidipine 20/10 mg film-coated tablets, Krka Slovenia (test product, T) and the reference product Carmen® ACE film-coated tablets (Recordati, EU).

The applicant stated that the bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

The objective of this study was to compare the rate and extent of absorption of the test product versus the reference product administered to healthy male volunteers in a single-dose, randomized, 2-way cross-over study under fasting conditions.

Based on the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), a single-dose comparative bioavailability study is adequate to demonstrate bioequivalence of an orally administered immediate-release formulation with systemic action. Bioequivalence was tested under fasting conditions. Crossover design was used to overcome the variability between subjects. The washout period between doses was considered sufficient (more than 10 times elimination half-life ($t_{1/2}$) to prevent carry-over effects of the treatments.

For both enalapril and lercanidipine blood samples were taken pre- and post-administration at appropriate time intervals.

The study population included Caucasian, non-smoker healthy male subjects.

Determination of enalapril in plasma samples was performed using validated LC/MS/MS, while that of lercanidipine validated chiral LC/MS/MS method.

As pharmacokinetic variables, C_{max}, AUC_t, AUC_i, residual area, T_{max}, T_{half} and K_{el} for enalapril, and lercanidipine enantiomers were determined from individual plasma concentration – time profiles using model-independent approach.

ANOVA was performed on log-transformed pharmacokinetic parameters C_{max}, AUC_t and AUC_{inf}. To conclude bioequivalence two one sided 90% confidence intervals were calculated for test by reference ratio of geometric least square mean of C_{max}, AUC_t.

The results are shown in the following Tables.

Enalapril

Parameter	Ratio (T/R)	Confidence intervals
AUC_t	98.99%	95.30% – 102.82%
AUC_i	99.05%	95.44% – 102.81%
C_{max}	94.42%	89.52% – 99.58%

S-Lercanidipine

Parameter	Ratio (T/R)	Confidence intervals
AUC_t	95.98%	89.81% – 102.58%
AUC_i	96.18%	90.04% – 102.73%
C_{max}	90.71%	82.05% – 100.29%

R-Lercanidipine

Parameter	Ratio (T/R)	Confidence intervals
AUC_t	92.98%	86.20% – 100.29%
AUC_i	93.39%	86.80% – 100.48%
C_{max}	88.65%	80.04% – 98.20%

The results of the study show that all the 90% confidence intervals for the log-transformed parameters AUC_{0-t} and C_{max} for enalapril and lercanidipine were within the 80-125% acceptable range. Thus, the test and the reference products are bioequivalent.

Biowaiver

The bioequivalence study was carried out with the highest strength (enalapril/lercanidipine 20/10 mg film-coated tablets, Krka Slovenia (test product, T) and the reference product ® Carmen® ACE film-coated tablets (Recordati, EU).

The applicant was seeking biowaiver for other strength by stating that all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) concerning biowaiver were met:

- the pharmaceutical products were manufactured by the same manufacturing process;
- both enalapril and Lercanidipine had a linear drug input over the developed dose range;
- the formulations are dose-proportional;
- *in vitro* dissolution testing at the required pH values showed similarity of dissolution profiles.

Thus, the results from the 20/10 mg film-coated tablet can be extrapolated to the 10/10 film-coated tablet, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, Rev. 1/ Corr **.

IV.3 Pharmacodynamics

No new studies were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of enalapril, and lercanidipine. Moreover, bioequivalence to a marketed reference product has been established.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Discussion on the clinical aspects

The application contains an adequate review of published clinical data and the bioequivalence to the chosen reference product has been successfully proven.

From clinical aspects the products are approvable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This decentralised procedure applications concerns enalapril/lercanidipine 10 mg/10 mg and 20 mg/10 mg fixed combination film-coated tablets. The applicant and the future holder of authorisation is Krka d.d. (Slovenia).

The legal basis of this application was Article 10(1) of the of the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (i.e. generic application).

The applicant has successfully proven the bioequivalence of the submitted 20 mg/10 mg strength to the reference product Carmen® ACE film-coated tablets (Recordati) that has been granted marketing authorisation in the European Economic Area. Having the biowaiver criteria met, the bioequivalence could be extended to the lower, 10 mg/10 mg strength.

The submitted documentation is administratively adequate and scientifically sound. The quality of the products is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted the marketing authorisation for Elernap (in Austria: Enalapril/Lercanidipine Krka, in Bulgaria and Czech Republic Lenap, in Lithuania Elymo) 10 mg/10 mg and 20 mg/10 mg film-coated tablets.

Elernap 10 mg/10 mg and 20 mg/10 ml film-coated tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by lercanidipine 10 or 20 mg alone.

V.1 Conditions for the marketing authorisation

Requirements for specific post-marketing obligations

Not needed.

Pharmacovigilance system

The applicant has provided the Summary of the Pharmacovigilance System of Krka d.d., Novo mesto which fulfils the requirements and stated that the marketing authorisation holder has the services of a qualified person responsible for pharmacovigilance (QPPV) as well as the necessary means for the notification of any adverse reaction suspected, occurring either in the Community or in a third country. The member state of the QPPV residence and the location of the Pharmacovigilance System Master File is Hungary.

Risk Management Plan

The submitted Risk Management Plan is acceptable. The routine risk minimisation measures are adequate to deal with the safety concerns.

Periodic Safety Update Report (PSUR)

The fix combination of enalapril maleate and lercanidipine is included in the present European Union Reference Dates (EURD) list. The PSUR submission should be aligned with the requirements (cycle, reference date, data lock point) published on the list. However, PSUR submission is not requested for products referred to in Article 10(1) of the Directive 2001/83/EC (generics). Thus, the marketing authorisation holder of Elernap film-coated tablets should not submit PSURs but should follow the actual EURD lists continuously to recognise any change.

Legal status

Prescription-only medicine.

V. 2 Summary of Product Characteristics (SmPC)

The SmPC is, from both pharmaceutical and medical aspects, acceptable.

V.3 Package Leaflet and user testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached