National Institute of Pharmacy
Directorate
of the National Institute for Quality- and Organizational Development in Healthcare and Medicines
Budapest, Hungary

GYEMSZI
Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet

Public Assessment Report

Name of the Product:

Co-Dalnessa

2 mg/0.625 mg/5 mg tablets
4 mg/1.25 mg/5 mg tablets
4 mg/1.25 mg/10 mg tablets
8 mg/2.5 mg/5 mg tablets
8 mg/2.5 mg/10 mg tablets

(perindopril tert-butylamine/indapamide/amlodipine besylate)

Procedure numbers:

HU/H/0342/001-005/DC

Marketing authorisation holder: Krka, d.d.

Date: 21 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 perindopril (as tert-butylamine)/indapamide/amlodipine (as besylate) 2 mg/0.625 mg/5 mg, 4 mg/1.25 mg/5 mg, 4 mg/1.25 mg/10 mg, 8 mg/2.5 mg/5 mg, 8 mg/2.5 mg/10 mg under the name of Co-Dalnessa (in certain member states Co-Amlessa) tablets. The holder of the marketing authorisation is Krka, d.d., Novo Mesto, Slovenia.

The excipient(s) of the tablets are sodium hydrogen carbonate, microcrystalline cellulose (E460), pregelatinised starch (Type 1500), sodium starch glycolate (Type A), colloidal anhydrous silica, magnesium stearate (E572) and calcium chloride hexahydrate.

The appearance of the tablets is as follows:

- 2 mg/5 mg/0.625 mg tablets: white to almost white, oval, biconvex, scored on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses;
- 4 mg/5 mg/1.25 mg tablets: white to almost white, round, slightly biconvex, with bevel edges;
- 4 mg/10 mg/1.25 mg tablets: white to almost white, oval, biconvex, scored on one side; The tablets can be divided into equal doses;
- 8 mg/5 mg/2.5 mg tablets: white to almost white, round, biconvex, with bevel edges;
- 8 mg/10 mg/2.5 mg tablets: white to almost white, round, biconvex, scored on one side with bevel edges. The tablets can be divided into equal doses.

The tablets are available in boxes of in a blister.

Co-Dalnessa tablets are prescribed for treatment of high blood pressure (hypertension). All three active principles help to control high blood pressure (hypertension). Patients already taking perindopril/indapamide and amlodipine from separate tablets may receive one tablet of Co-Dalnessa instead, which contains all three ingredients.

Co-Dalnessa tablets represent a combination of three active ingredients perindopril, indapamide and amlodipine. Perindopril is an ACE (angiotensin converting enzyme) inhibitor. Indapamide is a diuretic. Amlodipine is a calcium antagonist (which belongs to a class of medicines called dihydropyridines).

In patients with high blood pressure perindopril and amlodipine works by relaxing blood vessels, so that blood passes through them more easily. Indapamide increases the amount of urine produced by the kidneys. Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.

What should be known before taking Co-Dalnessa tablets

Do not take Co-Dalnessa tablets who

- are allergic to perindopril or any other ACE inhibitor, or to indapamide or any other sulphonamides, amlodipine besylate or any other dihydropyridines, or any of the other ingredients of the Co-Dalnessa tablets,
- have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or those or their family member have had these symptoms in any other circumstances (a condition called angioedema),
- have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain),
- have a severe or moderate kidney disease or are receiving dialysis,
- have low or high blood potassium level,
- are suspected of having untreated decompensated heart failure (severe water retention, difficulty in breathing),
- have cardiogenic shock (when the heart is unable to supply sufficient blood to the body), aortic stenosis (narrowing of the main blood vessels leading from the heart) or unstable angina (chest pain that may occur when resting),
- have severe low blood pressure (severe hypotension),
- suffer from heart failure (the heart fails to pump blood adequately resulting in the shortness of breath or peripheral swellings such as swelling of the legs, ankles or feet) after an acute heart attack,
- are more than 3 months pregnant (it is also better to avoid Co-Dalnesa tablets in early pregnancy - see “Pregnancy and Breast-feeding”),
- are breast-feeding.

Warnings and precautions

Consult their doctos before taking Co-Dalnessa tablets who

- have heart attack recently,
- have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- have heart failure,
- have any other heart problems or problems with your kidneys,
- have severe increase in blood pressure (hypertensive crisis),
- have liver problems,
- you suffer from a collagen disease (skin disease) such as systemic lupus erythematosus or scleroderma,
- have atherosclerosis (hardening of the arteries),
- suffer from hyperparathyroidism (overactive parathyroid gland),
- suffer from gout,
- have diabetes,
- are on a salt restricted diet or use salt substitutes which contain potassium,
- take lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with

Co-Dalnessa should be avoided (see also "Taking other medicines"),
- are elderly and your dose needs to be increased.

If the pateint thinks she is pregnant (or might become) pregnant, sonsult her doctor for Co-Dalnessa tablets are not recommended in early pregnancy, and must not be taken after 3 months pregnancy, as it may cause serious harm to the baby if used at that stage (see also "Pregnancy and Breast-feeding").

Who is taking Co-Dalnessa tablets, should also inform the doctor or the medical staff if
- is to undergo anaesthesia and/or surgery,
- has recently suffered from diarrhoea or vomiting, or ise dehydrated,
- is to undergo dialysis or LDL apheresis (which is removal of cholesterol from the blood by a machine),
- is going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings,
- is to undergo a medical test that requires injection of an iodinated contrast agent (a substance that makes organs like kidney or stomach visible on an X-ray).

Athletes should be aware that Co-Dalnessa tablets contain an active ingredient (indapamide) which may give a positive reaction in drug tests.

Children and adolescents

Co-Dalnessa tablets are not recommended for use in children and adolescents.

Other medicines and Co-Dalnessa tablets

Taking of Co-Dalnessa tablets should be avoided together with:
- lithium (used to treat depression),
- potassium-sparing diuretics (spironolactone, triamterene), potassium salts.

Treatment with Co-Dalnessa tablets can be affected by other medicines.

Patients who take any of the following medicines should inform their doctor for special care may be required:
- other medicines for treating high blood pressure,
- procainamide (for the treatment of an irregular heart beat),
- allopurinol (for the treatment of gout),
- terfenadine or astemizole (antihistamines for hay fever or allergies),
- corticosteroids used to treat various conditions including severe asthma and rheumatoid
- arthritis,
- immunosuppressants used for the treatment of auto-immune disorders or following transplant surgery to prevent rejection (e.g. ciclosporin),
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV),
- medicines for the treatment of cancer,
- ketoconazole, itraconazole (anti-fungal medicines)

- rifampicin, erythromycin, clarithromycin (antibiotics),
- halofantrine (used to treat certain types of malaria),
- pentamidine (used to treat pneumonia),
- injectable gold (used to treat rhumatoid polyarthritis),
- vincamine (used to treat symptomatic cognitive disorders in elderly including memory loss),
- bepridil, verapamil, diltiazem (heart medicines),
- sultopride (for the treatment of psychoses),
- medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol),
- digoxin or other cardiac glycosides (for the treatment of heart problems),
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis),
- medicines to treat diabetes such as insulin or metformin,
- calcium including calcium supplements,
- stimulant laxatives (e.g. senna),
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) or high dose salicylates (e.g. aspirin),
- amphotericin B by injection (to treat severe fungal disease),
- medicines to treat mental disorders such as depression, anxiety, schizophrenia…(e.g. tricyclic antidepressants, neuroleptics),
- tetracosactide (to treat Crohn's disease),
- hypericum perforatum (St. John's Wort),
- dantrolene (infusion for severe body temperature abnormalities),
- simvastatin (a cholesterol lowering medicine),
- anaestetics.

Taking Co-Dalnessa tablets with food and drink

It is preferable to take Co-Dalnessa tablets before a meal.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, consult their doctor for advice before taking this medicine.

Pregnancy: women must tell their doctor if they think they are (or might become) pregnant. The doctor will normally advise them to stop taking Co-Dalnessa tablets before they might become pregnant or as soon as they recognised they pregnant and will advise taking another medicine. Co-Dalnessa tablets are 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.

Breast-feeding: who are breast-feeding or about to start breast-feeding should consult their doctor. Co-Dalnessa tablets are contra-indicated for mothers who are breast-feeding, and their doctor may choose another treatment for those who wish to breast-feed, especially if the baby

is newborn, or was born prematurely.

Driving and using machines

Co-Dalnessa tablets do not affect alertness but patients might experience dizziness or weakness due to low blood pressure which could affect their ability to drive or operate machinery. Nevertheless, patients taking Co-Dalnessa tablets are advised not to drive a car or operate machinery until they know how Co-Dalnessa tablets affect them.

How to take Co-Dalnessa tablets

The recommended dose is one tablet once a day. It should be taken preferably in the morning and before a meal, swallowed with a glass of water.

If needed, Co-Dalnessa 4 mg/10 mg/1.25 mg and Co-Dalnessa 8 mg/10 mg/2.5 mg tablets can be divided into equal doses. One can split these tablets by putting them on a flat surface with the scoreline facing upwards. Then press with two fingers on both ends of the tablet.

The doctor will decide on the correct dose for individual patients. Co-Dalnessa tablets are prescribed for patients already taking perindopril/indapamide and amlodipine from separate tablets.

What to do if more Co-Dalnessa tablets are taken than prescribed

If someone takes too many tablets, he/she should contact the doctor or the nearest hospital casualty department immediately. In case of overdose, the most likely effect is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

What to do if taking Co-Dalnessa tablets was forgotten

It is important to take the medicine every day as regular treatment is more effective. However, if someone forgets to take a dose of Co-Dalnessa tablets, take the next dose at the usual time. It should not be taken a double dose to catch up the forgotten tablet.

Stopping the use of Co-Dalnessa tablets

As the treatment for high blood pressure is usually life-long, the patient should consult his/her doctor before stopping taking this medicinal product.

Possible side effects

Like all medicines, Co-Dalnessa tablets can cause side effects, although not everybody gets them.

If one experiences any of the following, should stop taking the medicinal product at once and

consult the doctor immediately:
- symptoms of allergic reaction such as swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
- severe dizziness or fainting,
- unusual fast or irregular heart beat.

In decreasing order of frequency, other side effects can include:

Common (may affect up to 1 in 10 people): headache, feelings of dizziness, vertigo, pins and needles, somnolence (sleepiness), vision disturbances (includin double vision), light-headedness due to low blood pressure, tinnitus (sensation of noises in the ears), low blood pressure, palpitations (very fast heartbeat), flushing (hot or warm feeling in your face), shortness of breath, cough, gastro-intestinal disorders (nausea, epigastric pain, anorexia, vomiting, abdominal pain, taste disturbances, dry mouth, dyspepsia or difficulty of digestion, diarrhoea, constipation), cramps, oedema (swelling of legs or ankles), feeling of tiredness.

Uncommon (may affect up to 1 in 100 people): allergic reactions (such as skin rashes, itching), mood swings, sleep disturbances, sleeplessness, depression, trembling, loss of pain sensation, syncope (temporary loss of consciousness), rhinitis (blocked up or runny nose), bronchospasm (tightening of the chest, wheezing and shortness of breath), changed bowel habits, angioedema (symptoms such as wheezing, swelling of the face or tongue), urticaria, purpura (red pinpoints on skin), sweating, hair loss, red or discoloured patches on skin, back, muscle or joint pain, kidney problems, increased need to urinate especially during the night, impotence, breast enlargement in men, chest pain, pain, general feeling of being unwell, weight increase or decrease,

Very rare (may affect up to 1 in 10,000 people): high blood sugar, confusion, cardiovascular disorders (irregular heart beat, angina, heart attack), eosinophilic pneumonia (a rare type of pneumonia), swelling of the gums, abdominal bloating (gastritis), peripheral neuropathy (disease that produces loss of sensations, pain, inability to control muscles), increased muscle tension, severe skin manifestations such as erythema multiforme. If the patient suffers from systemic lupus erythematosus (a type of collagen disease), this might get worse. Cases of photosensitivity reactions (change in skin appearance) after exposure to the sun or artificial UVA have also been reported.

Not known frequency (it can not be estimated from the available data):
- life-threatening irregular heart-beat (Torsade de pointes),
- disorders of the blood, kidney, liver or pancreas and changes in laboratory parameters (blood tests) can occur. Ther doctor may require the blood tests to monitor the patient's condition,
- in cases of hepatic insufficiency (liver problems), there is a possibility of onset of hepatic encephalopathy (degenerative disease in the brain).

How to store Co-Dalnessa tablets

Do not store them above 30°C. Store in the original package in order to protect from light and moisture.

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

Scientific discussion

This module reflects the scientific discussion for the approval of Co-Dalnessa 2 mg/0.625 mg/5 mg, 4 mg/1.25 mg/5 mg, 4 mg/1.25 mg/5 mg, 8 mg/2.5 mg/5 mg and 8 mg/2.5 mg/10 mg tablets.
The procedure was finalised at 23 October 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 95th Act 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 State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Estonia, Latvia, Lithuania, Poland and Slovakia) concerned the combination product of perindopril/indapamide/amlodipine tablets

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Co-Dalnessa (in certain concerned member states Co-Amlessa) 2 mg/0,625mg/5mg, 4 mg/1,25mg/5mg, 4 mg/1,25mg/10mg, 8 mg/2,5mg/5mg, 8 mg/2,5mg/10mg perindopril/indapamide/amlodipine tablets. The marketing authorisation holder has been Krka d.d., Novo mesto, Slovenia.

The products are indicated as substitution therapy for the treatment of essential hypertension, in patients already controlled with perindopril/indapamide and amlodipine, given concurrently at the same dose level as in the combination.

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

The marketing authorisation has been granted pursuant to Article 10(b) of Directive 2001/83/EC (fixed combination). For the claimed indication no new clinical or preclinical data, other than supporting literature where necessary, were included. The applicant has adequately demonstrated bioequivalence between the combination and the individual reference products in two studies.

The product development rationale as outlined by the applicant is primarily related to the benefits of fixed combination therapy in terms of simplification of the therapeutic regimen. Furthermore, combining the three agents may not only achieve better blood pressure control but increase tolerability, due to their complementary mechanisms of action. Angiotensin-converting enzyme inhibitors (ACEI) with a dihydropyridine calcium-channel blocker (CCB) significantly reduce the incidence of CCB-related vasodilatory oedema and diuretic-related hypokalemia.

II. QUALITY ASPECTS

II.1 Introduction

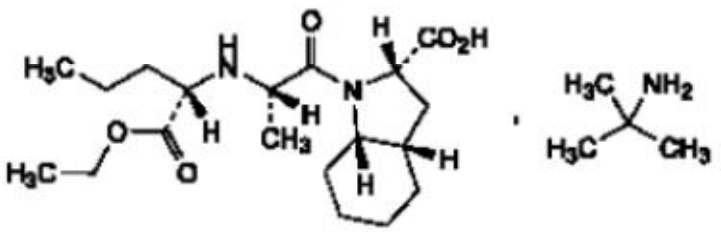
This assessment concerns the decentralised application of Co-Dalnessa 2 mg/0.625 mg/5 mg, 4 mg/1.25 mg/5 mg, 4 mg/1.25 mg/10 mg, 8 mg/2.5 mg/5 mg and 8 mg/2.5 mg/10 mg tablets. The legal basis of the submission has been Article 10.b of Directive 2001/83/EC, i.e. "fixed combination". The products have been developed by Krka, d.d., Slovenia.

2.2 Drug Substance

2.2.1 Perindopril tert-butylamine (erbumine)

Data on the quality and manufacture of the Perindopril erbumine 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: perindopril erbumine
Chemical name: 2-Methylpropan-2-amine (2S,3aS,7aS)-1-((S)-2-((S)-1-ethoxy-1-oxopentan-2ylamino)propanoyl)octahydro-1H-indole-2-carboxylate
Structure:



The active substance is a white or almost white, slightly hygroscopic crystalline powder and is freely soluble in water and in ethanol. The molecule has five asymmetric centres, thus, theoretically 32 stereo isomers can exist. It shows polymorphism. The manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by elementary analysis, mass spectra, NMR spectra and by FT-IR spectra. Polymorphism is controlled by X-ray powder diffraction test which is routinely performed as an in-process control to demonstrate the consistency of the manufacturing process.

The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph; additional specification has been set for residual solvents (GC) and heavy metals.

The Ph. Eur. specification includes the following tests for perindopril erbumine: appearance, solubility, identification (specific optical rotation, IR, TLC), impurity A (TLC), stereochemical purity (HPLC), related substances (HPLC), water content, sulphated ash and assay (titration).

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used for the control of the substance are adequately characterized.

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.

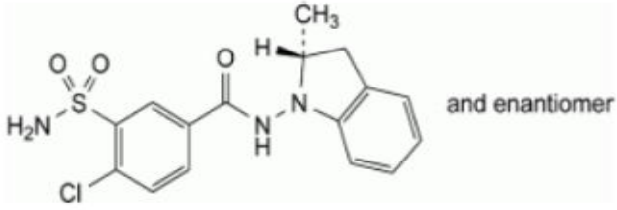
During the stability studies no significant changes in any parameters were observed. The proposed retest period of 2 years with the storage condition: "Do not store above 25°C. Store in the original packaging, in order to protect from moisture." is supported by the submitted stability data.

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

II.2.2 Indapamide

Data on the quality and manufacture of the Indapamide active substance were provided by the applicant's using the Certificate of the European Pharmacopoeia (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: indapamide
Chemical name: 4-chloro-N-[2'(R,S)-methyl-1'-indolinyl]-3-sulfamoylbenzamide
Structure:



The active substance is a white or almost white powder and is practically insoluble in water.

The substance is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents and particle size.

The Ph. Eur. specification includes the following tests for indapamide: appearance, solubility, identification (IR, UV spectrophotometry, TLC), optical rotation, related substances (HPLC), impurity A (HPLC), heavy metals, water content, sulphated ash, assay (HPLC). Residual solvents (GC) and particle size are also controlled.

Methods for testing the residual solvents and particle size distribution – which are not described in the Pharmacopoeia – are adequately drawn up and sufficiently validated.

Reference materials used for the control of the substance are adequately characterized.

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

The re-test period mentioned on the CEP is five years if the substance is stored in a double polyethylene bag inside a fiber drum.

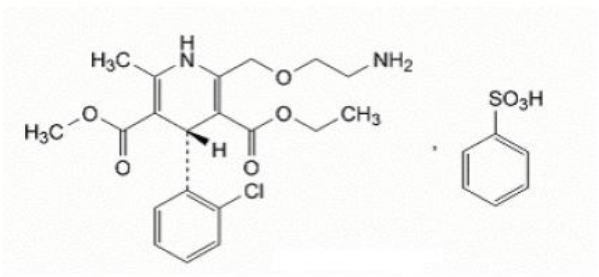
Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.2.3 Amlodipine besylate

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: amlodipine besilate
Chemical name: 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.

Structure:



The active substance is a white or almost white powder and is slightly soluble in water, freely soluble in methanol and sparingly soluble in ethanol.

The substance is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents.
The Ph. Eur. specification includes the following tests for amlodipine besylate: appearance, solubility, identification (IR), optical rotation, related substances (HPLC), water content, sulphated ash and assay (HPLC). Residual solvent method (GC) not described in the Pharmacopoeia is adequately drawn up and sufficiently validated.

Reference materials used for the control of the substance are adequately characterized.

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

The re-test period mentioned in the CEP is 60 months if the substance is stored in a double polyethylene bag (inner translucent bag and outer black bag) inside a fiber drum.

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

II.3 Medicinal Product

The medicinal products are tablets containing fixed combinations of perindopril erbumine (α polymorphic forms), indapamide and amlodipine besylate in different strengths.

The aim of the pharmaceutical development activities was to combine the currently approved doses of perindopril erbumine, indapamide and amlodipine into a single tablet. This intends to support patient adherence to treatment. Moreover the proposed medicinal products are claimed to be bioequivalent to reference products Pretanix Komb Forte 8 mg/ 2.5 mg tablets (perindopril erbumine/indapamide, Les laboratoires Servier Industrie, France or Servier Industries Ltd., Ireland) and Istin 10 mg tablets (amlodipine besylate, Pfizer).

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 products.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained:

- the 2 mg/0.625 mg/5 mg strength: white to almost white, oval, biconvex one-side scored tablets. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses;
- the 4 mg/1.25 mg/10 mg strength: white to almost white, oval, biconvex, one-side scored tablets. The tablets can be divided into equal doses;
- the 4 mg/1.25 mg/5mg strength: white to almost white, round, slightly biconvex tablets with bevel edges,;
- the 8 mg/2.5 mg /5 mg strength: white to almost white, round, biconvex tablets with bevel edges;
- the 8 mg/2.5 mg/10 mg strength: white to almost white, round, biconvex, one-side scored tablets with bevel edges. The tablets can be divided into equal doses.

Detailed 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 excipients used in the finished product are calcium chloride hexahydrate, microcrystalline cellulose, pregelatinised maize starch, sodium starch glycolate, sodium hydrogen carbonate, colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. regarding the risk of TSE has been demonstrated by the applicant.

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 International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. 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.

The container closure system of the product is OPA/Al/PVC//Al blisters and box. Specifications and quality certificates for all packaging components are enclosed. Certificates of analysis justifying the conformity to the relevant Ph. Eur. monograph and compliance with the Regulation 10/2011/EC of the European Commission are provided.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months is approved with the following storage

condition: "store below 30°C in the original packaging in order to protect from moisture and light".

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

I.1 II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application is based on the bioequivalence of this combination product with the reference products, for substitution indication. Thus, submission of new non-clinical studies has not been required.

The pharmaco-toxicological properties of perindopril, indapamide and amlodipine 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 perindopril, indapamide and amlodipine.

III.2 Pharmacology

Perindopril is an ACE inhibitor, indapamide is a thiazide-like diuretic and amlodipine is a dihydropyridine calcium channel blocker. All three active substances are well-known compounds. No further information was provided regarding the pharmacology of perindopril, indapamide and amlodipine.

III.3 Pharmacokinetics

No pharmacokinetic studies were performed in animals with the combination of perindopril/indapamide/amlodipine were found available in literature by the applicant. The application contains only data on perindopril, indapamide and amlodipine alone.

III.4 Toxicology

No toxicity studies were submitted by the applicant for the proposed fixed combination. Published information on toxicological studies with perindopril, indapamide and amlodipine was the basis for the evaluation.

The kidney is a common target organ for all these three substances, therefore the potential for renal toxicity may be expected to be greater with the perindopril/indapamide/amlodipine combination compared to the individual components. However, all active substances are well established, it is a substitution indication, and adequate recommendations on renal impairment can be given based on available information.

Due to its mechanism of action, the ACE inhibitors, as perindopril, are not recommended during the first trimester of pregnancy and contraindicated during the second and third trimesters. Retardation of ossification and low body weight were detected in development toxicity studies with indapamide. Furthermore, the applicant concluded that amlodipine caused effect on the endocrine system (e.g. decrease hormone levels, decrease spermatids production and amount of Sertoli cells nuclei, etc...) and pregnancy (e.g. prolonged gestational period, in-

crease stillborn pups, decrease litter size). From the information presented, it is not possible to conclude the relevance of these effects to human and the possibility to induce additive adverse effects on reproduction, after a treatment with perindopril + indapamide + amlodipine.

Safety of the combination will be established by the human bioequivalence study, if the bio-equivalence with products of established use is proven.

III.5 Ecotoxicity/environmental risk assessment

The combination product is indicated for a substitution indication and as such will replace use of the co-administered single products. Thus the exposure of the environment to perindopril, to indapamide and to amlodipine will not increase by use of this product and, therefore, no environmental risk assessment was required.

II.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of perindopril, indapamide and amlodipine are well-known. As the combination is only for substitution therapy there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The product development rationale as outlined by the applicant was primarily related to the benefits of fixed combination therapy in terms of simplification of the therapeutic regimen. Furthermore, combining the three agents may not only achieve better blood pressure control but increase tolerability, due to their complementary mechanisms of action. ACEI with a dihydropyridine CCB significantly reduces the incidence of CCB-related vasodilatory oedema and diuretic-related hypokalemia.

Perindopril, indapamide and amlodipine have complementary mechanisms of action in reducing BP and synergistic cardioprotective effects are expected.

The thiazide diuretics (as well as indapamide), CCBs and ACE inhibitors can adequately lower the blood pressure. To take into consideration that the main benefits of antihypertensive treatment are due to lowering of BP per se, independent of the drugs employed, all of them are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combinations.

The combinations of perindopril with amlodipine or indapamide constitute recommended combination of priority use. By combining such agents routinely used in arterial hypertension, fixed-combination perindopril/indapamide/amlodipine could improve adherence to uncontrolled hypertensive patients. The impact on the optimization of the management of hypertension has been already recognized by the European guidelines.

For the combination product is indicated as substitution therapy for those patients who are adequately controlled with perindopril, indapamide and amlodipine given concurrently, at the same dose level as in the combination, the application was based on two bioequivalence studies.

IV.2 Pharmacokinetics

IV.2.1 Literature data

The application contained literature reviews for the pharmacokinetics of the individual components.

Perindopril:

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a pro-drug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to

active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril should be administered orally in a single daily dose in the morning before a meal.

A linear relationship has been demonstrated between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Indapamide

Indapamide is rapidly and completely absorbed from the digestive tract. The peak plasma level is reached in humans approximately one hour after oral administration of the product. Plasma protein binding is 79 %.

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. Its bioavailability is not influenced by food. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

The pharmacokinetics of indapamide is unchanged in patients with renal insufficiency.

Perindopril kinetics is modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

As with all calcium antagonists, the half-life of amlodipine is prolonged in patients with impaired liver function.

IV.2.2 Bioequivalence studies

To support the application, the applicant submitted two bioequivalence study reports. The bioequivalence studies were carried out with the 8 mg/2.5 mg/10 mg and with 4mg/1.25mg/10 mg strengths.

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

Study design chosen and main objective of the study with the 8 mg/2.5 mg/10 mg strength

The clinical development performed by the applicant comprised of an open-label, single-dose, two-way, crossover study, during which the subjects received the fixed dose combination of perindopril/indapamide/amlodipine 8 mg/2.5 mg/10 mg tablets as Test treatment (T) *versus* concomitant application of one Pretanix Komb Forte® 8 mg/2.5 mg tablets ((Les Laboratoires Servier, France) and one Istin™ 10 mg tablet (Pfizer Limited) as Reference treatment (R) to healthy male volunteers under fasting conditions.

Perindopril, indapamide and amlodipine blood samples were collected prior to administration and pots-dosage at appropriate time intervals.

Determination of perindopril, indapamide and amlodipine was performed using validated LC-MS/MS methods.

As pharmacokinetic parameters, $C_{max,}$ AUC_t, AUC_{0-72}, AUC_i, R_{AUC} (rezidual area), T_{max}, T_{half}, and K_{el} for perindopril, indapamide and amlodipine were determined from individual plasma concentration *versus* time profiles.

The comparison of test and reference product was performed by the bioequivalence Guideline in force during the evaluation: After ln-transformation for $C_{max,}$ AUC_t, AUC_{0-72} and AUC_i ANOVA test was performed and the classical 90% (shortest) confidence intervals (CIs) were calculated for the intra-individual ratios. In the ANOVA (analysis of variance) model 4 factors were included: sequence, subject within sequence, formulation and period. Point estimates for the ratio of average bioequivalence were also determined for the above mentioned parameters.

Bioequivalence was concluded if the 90% CIs for the ratio (T/R) of the LS-Means of $C_{max,}$ AUC_t, AUC_{0-72} and AUC_i parameters were included within interval 80-125%.

Summary of results of this bioequivalence study

Parameter	Ratio T/R %	CI %
P e r i n d o p r i l		
AUC_t	101.88	97.57 – 106.38
C_{max}	107.18	98.22 – 116.94
I n d a p a m I d e		
AUC_t	102.83	101.09 – 104.61
C_{max}	101.34	98.53 – 104.22
A m l o d i p i n e		
AUC_{0-72}	103.88	101.24 – 106.58
C_{max}	103.01	100.08 – 106.02

Based on the results, perindopril/indapamide/amlodipine 8 mg/2.5 mg/10 mg Krka tablets formulation, which was tested in comparison with coadministration of Pretanix® Komb Forte 8 mg/2.5 mg tablets (Les Laboratoires Servier France) (perindopril as arginine/indapamide) and one Istin™ (amlodipine as besilate) 10 mg tablets (Pfizer Limited) (comparative treatment) administered simultaneously are bioequivalent under fasting condition

Study design chosen and main objective of the study with the 4 mg/1.25 mg/10 mg strength

The clinical development performed by the applicant comprised of an open-label, single-dose, two-way, crossover study, during which the subjects received the fixed dose combination of Perindopril/indapamide/amlodipine 4 mg/1.25 mg/10 mg tablets as test treatment (T) versus concomitant application of one BiPretarax® N 5mg/1.25 mg film-coated tablets (Les Laboratoires Servier France) and one Istin™ 10 mg tablet **(Pfizer Limited)** as Reference treatment (R) to healthy male volunteers under fasting conditions.

For perindopril, indapamide and amlodipine blood samples were collected prior to drug administration and post-dose at appropriate time-intervals.

Determination of perindopril, indapamide and amlodipine was performed using validated LC-MS/MS methods.

A pharmacokinetic parameters, $C_{max,}$ AUC_t, AUC_{0-72}, AUC_i, R_{AUC} (rezidual area), T_{max}, T_{half}, and K_{el} for perindopril, indapamide and amlodipine were determined from individual plasma concentration *versus* time profiles. Average- and ln concentration-time plots for (A) and (B) treatments were constructed.

The comparison of test and reference product was performed by the bioequivalence Guideline in force during the evaluation: After ln-transformation for $C_{max,}$ AUC_t, AUC_{0-72} and AUC_i ANOVA test was performed and the classical 90% confidence intervals (CIs) were calculated for the intra-individual ratios. In the ANOVA (analysis of variance) model 4 factors were included: sequence, subject within sequence, formulation and period. Point estimates for the ratio of average bioequivalence were also determined for the above mentioned parameters.

Bioequivalence was concluded if the 90% CIs for the ratio (test/reference) of the LS-Means of $C_{max,}$ AUC_t, AUC_{0-72} and AUC_i parameters were included within interval 80 – 125%.

Results of this study are shown below. Based on the results, perindopril/indapamide/amlodipine 4 mg/1.25 mg/10 mg Krka tablets formulation, which was tested in comparison with coadministration of BiPreterax® N 5 mg/1.25 mg film-coated tablets (Les Laboratoires Servier France) (perindopril as arginine/indapamide) and one IstinTM (amlodipine as besilate) 10 mg tablets (Pfizer Limited), i.e. the comparative treatment administered simultaneously are bioequivalent under fasting condition

Parameter	Ratio T/R %	CI %
P e r i n d o p r i l		
AUC_{0-t}	101.63	98.18 – 105.20
C_{max}	98.30	90.66 – 106.58
I n d a p a m I d e		
AUC_{0-t}	101.69	99.75 – 103.68
C_{max}	101.24	97.88 – 104.62
A m l o d i p i n e		
AUC_{0-72}	101.96	99.50 – 104.48
C_{max}	101.96	98.44 – 105.61

Biowaiver for the other strengths

The results of bioequivalence studies with perindopril/indapamide/amlodipine 8 mg/2.5 mg/10 mg and 4 mg/1.25 mg/10 mg strength can be extrapolated to other strengths: 8 mg/2.5 mg/5 mg, 4 mg/1.25 mg/5 mg, 2 mg/0.625 mg/5 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6, for all relevant requirements were met:

- the pharmaceutical products were manufactured by the same manufacturing process;
- all active substances (perindopril erbumine, indapamide and amlodipine) express linear pharmacokinetics over the therapeutic dose range,
- dose-proportional formulations,
- *in vitro* dissolution testing at the required pH values has shown similarity of dissolution profiles.

IV.3 Pharmacodynamics

Clinical pharmacology studies specifically designed to evaluate the pharmacodynamics of the fixed combination of perindopril/indapamide/amlodipine were not performed. The application was, for the intended indication substitution therapy, based on the bioequivalence studies.

IV.4 Clinical efficacy

Perindopril, indapamide and amlodipine have complementary mechanisms of action in reducing blood pressure and synergistic cardioprotective effects are expected.

The thiazide diuretics (as well as indapamide), CCBs and ACE inhibitors can adequately lower BP. To take into consideration that the main benefits of antihypertensive treatment are due to lowering of BP per se, independent of the drugs employed, all of them are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combinations.

The combinations of perindopril with amlodipine or indapamide constitute recommended combinations of priority use. By combining such agents routinely used in arterial hypertension, fixed-combination perindopril/indapamide/amlodipine could improve adherence to uncontrolled hypertensive patients. The impact on the optimization of the management of hypertension has been already recognized by the European guidelines.

Reducing cardiovascular events and also mortality remains the key goal in the management of hypertension. The effectiveness of perindopril has been widely demonstrated in morbidity-mortality clinical trials as monotherapy and particularly in combination therapy.

Combined analysis of clinical trials with perindopril in combination with indapamide or amlodipine confirmed a 13% reduction in all-cause mortality (95% CI 0.81-0.93, $p<0.0001$).

Based on IMS market expertise, perindopril/indapamide and amlodipine have been adequately co-prescribed. There is evidence of established use of the combination supporting the appli-

cant's claim. The applicant provided sufficient data to support the established use of this dosage combination.

Regarding the efficacy profile the proposed substitution indication and dosage for the triple combination is acceptable.

IV.-5 Clinical safety

Safety of perindopril and indapamide

The safety of perindopril/indapamide fixed combinations has been established for many years. Tolerability in hypertensive patients has been generally high, with low withdrawal rates and few side-effects being recorded. The most frequently noted adverse events are cough and headache, both of which are largely attributable to a class effect of ACE inhibition. The safety and tolerability was established that perindopril does not expose the patients to any additional adverse effects or interactions with concomitant drugs other than those known for each of these components already described. Better BP results of perindopril/indapamide were not obtained at the expense of a worsening tolerability.

Safety of perindopril and amlodipine

The use of ACE inhibitors with CCBs appears to improve the side effect profile of the CCB. As dihydropyridines are potent vasodilators, the most common adverse event associated with the CCB class, peripheral oedema, is reduced by co-administration of the two classes of agent. The reflex increase in heart rate possibly occurring during treatment with dihydropyridines, which might be manifested as palpitations, is prevented by concomitant blockade of the RAS. One might also expect reductions in CCB-associated flushing and headache, because lower doses of the CCB are generally adequate when these vasodilators are used in combination with a blocker of the RAS.

Safety of amlodipine and indapamide

In terms of safety, the combination amlodipine and indapamide regimens showed acceptable and comparable tolerability.

Post marketing experience

The applicant presented convincing safety data for amlodipine, perindopril/indapamide and combined use of perindopril/indapamide + amlodipine from the worldwide safety database .

IV.6 Discussion on the clinical aspects

The application concerns a fixed combination of perindopril, indapamide and amlodipine. The indication is substitution therapy for the treatment of essential hypertension, in patients al-

ready controlled with the combination of perindopril, indapamide and amlodipine, taken at the same dose level.

To support the request the applicant has adequately demonstrated bioequivalence between the combination and co-administered reference products: fixed dose combination of perindopril + indapamide and amlodipine as monocomponent.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present applications concerns Co-Dalnessa 2 mg/0.625 mg/5 mg, 4 mg/1.25 mg/5 mg, 4 mg/1.25 mg/10 mg, 8 mg/2.5 mg/5 mg and 8 mg/2.5 mg/10 mg (active principles: perindopril ter-butylamine/indapamide/amlodipine besylate) fixed combination tablets. The applicant and the future holder of authorisation is Krka d.d., Novo mesto (Slovenia).

The products are indicated as substitution therapy for the treatment of essential hypertension, in patients already controlled with perindopril/indapamide and amlodipine, given concurrently at the same dose level as in the combination.

The applicant claimed better patient adherence when fixed combination is used, moreover, submitted adequate proof on the co-prescription of the three active principles in certain member states.

To support the application, bioequivalence between the 8 mg/2.5 mg/10 mg strength and coadministered Pretanix Komb Forte® 8 mg/2.5 mg tablets (Les Laboratoires Servier France) (perindopril as arginine/indapamide) and Istin™ (amlodipine as besilate) 10 mg tablets (Pfizer Limited), as well as the 5 mg/2.5 mg/10 mg strength and coadministered BiPreterax® N 5 mg/1.25 mg film-coated tablets (Les Laboratoires Servier France) (perindopril as arginine/indapamide) and one Istin™ (amlodipine as besilate) 10 mg tablets (Pfizer Limited) has been proven.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product 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 marketing authorisation for Co-Dalnessa 2 mg/0.625 mg/5 mg, 4 mg/1.25 mg/5 mg, 4 mg/1.25 mg/10 mg, 8 mg/2.5 mg/5 mg and 8 mg/2.5 mg/10 mg.

V.1 Conditions for the marketing authorisation

Requirements for specific post-marketing obligations

Not needed.

Pharmacovigilance system

The applicant has provided a summary of the pharmacovigilance system, stating that the marketing authorisation holder has at its disposal a qualified person for pharmacovigilance (QPPV), and that this person has the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country. The con-

tact details of the QPPV are provided, as well as a statement on the location of the Pharmacovigilance Site Master File.

The Summary of the Pharmacovigilance System is considered acceptable.

Risk Management Plan

The submitted Risk Management Plap is approved. Detailed Summary of the Risk Management Plan for the health-care proffesionals can be found in a separate document (RMP Summary VI.).

Periodic Safety Update Report (PSUR)

The PSUR submission scheme should follow 2001/83/EC directive Article 107c (2) second subparagraph starting with 6-monthly PSUR. The list of European Union Reference Dates (EURD List) should be followed with attention for possible common Data Lock Point and PSUR cycle.

Legal status

In the RMS: 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
Y/N (version)						