OGYÉI Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet

1051 Budapest, Zrínyi utca 3.
Levélcím: 1372 Postafiók 450
Tel.: +36 1 886 9300, Fax: +36 1 886 9460
E-mail: ogyei@ogyei.gov.hu
Web: www.ogyei.gov.hu

Public Assessment Report

Name of the Product:

Prenessa-AS 5 mg tablets
Prenessa-AS 10 mg tablets

(perindopril arginine)

Procedure number: HU/H/0113/006-007/DC

Marketing authorisation holder: KRKA, d.d., Novo mesto

Date: 08. 12. 2021.

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LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Prenessa-AS 5 mg and 10 mg tablets. The holder of the marketing authorisation is KRKA, d.d., Novo mesto.

The active substance is perindopril arginine.

- Prenessa-AS 5 mg tablets: each tablet contains 5 mg perindopril arginine, equivalent to 3,395 mg perindopril.
- Prenessa-AS 10 mg tablets: each tablet contains 10 mg perindopril arginine, equivalent to 6,790 mg of perindopril.

The other ingredients are:

- calcium chloride hexahydrate; cellulose, microcrystalline; silica, colloidal anhydrous; magnesium stearate.

The appearance of the tablets is:
- The 5 mg tablets are white or almost white capsule-shaped tablets, scored on both sides. One side of the tablet is marked with V1 - with V on one side of the score line and 1 on the other side of the score line. Tablet dimensions: approximately 8 mm x 5 mm. The tablet can be divided into equal doses.
- The 10 mg tablets are white or almost white, round, biconvex tablets marked with V2 on one side of the tablet. Diameter: approximately 8 mm.

The tablets are available in packs in blisters.

Prenessa-AS contains perindopril arginine, which is an angiotensin converting enzyme (ACE) inhibitor. These work by widening the blood vessels, which makes it easier for the heart to pump blood through them.

Prenessa-AS 5 mg and 10 mg tablets are used:
- to treat high blood pressure (hypertension),
- to reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

Prenessa-AS 5 mg tablets are also used:
- to treat heart failure (a condition where the heart is unable to pump enough blood to meet the body’s needs).

What patients need to know before using Prenessa-AS

Patients must not take Prenessa-AS if they

- are allergic to perindopril, any other ACE inhibitor or any of the other ingredients of this medicine;
- have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if patients or a member of their family have had these symptoms in any other circumstances (a condition called angioedema);
- are more than 3 months pregnant (it is also better to avoid Prenessa-AS in early pregnancy);
- have diabetes or impaired kidney function and they are treated with a blood pressure lowering medicine containing aliskiren;
- are having dialysis or any other type of blood filtration. Depending on the machine that is used, Prenessa-AS may not be suitable for them;
- have kidney problems where the blood supply to their kidneys is reduced (renal artery stenosis);
- have taken or are currently taking sacubitril/valsartan, a medicine for heart failure, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased.

Warnings and precautions

Before taking Prenessa-AS patients sholud talk to their doctor or pharmacist if they:

- 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 any other heart problems;
- have liver problems;
- have kidney problems or if they are receiving dialysis;
- have abnormally increased levels of a hormone called aldosterone in their blood (primary aldosteronism);
- suffer from a collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma;
- have diabetes;
- are on a salt restricted diet or use salt substitutes which contain potassium;
- are to undergo anaesthesia and/or major surgery;
- are to undergo LDL apheresis (which is removal of cholesterol from their blood by a machine);
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings;
- have recently suffered from diarrhoea or vomiting, or are dehydrated;
- have been told by their doctor that they have an intolerance to some sugars;
- are taking any of the following medicines used to treat high blood pressure:

- an “angiotensin II receptor blocker" (ARBs) (also known as sartans- for example valsartan, telmisartan, irbesartan), in particular if they have diabetes-related kidney problems;
- aliskiren;

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

- are of black origin since they may have a higher risk of angioedema and this medicine may be less effective in lowering their blood pressure than in non-black patients;
- are taking any of the following medicines, the risk of angioedema is increased:
  - racecadotril (used to treat diarrhoea);
  - sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTOR inhibitors (used to avoid rejection of transplanted organs);
  - sacubitril (available as fixed-dose combination with valsartan), used to treat long-term heart failure, linagliptin, saxagliptin, sitagliptin, vildagliptin and other drugs belonging to the class of the also called gliptins (used to treat diabetes).

Angioedema
Angioedema (a severe allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing) has been reported in patients treated with ACE inhibitors, including Prenessa-AS. This may occur at any time during treatment. If patients develop such symptoms, they should stop taking Prenessa-AS and see a doctor immediately.

The doctor should be told if patients think they are (or might become) pregnant. Prenessa-AS is not recommended in early pregnancy, and must not be taken if patients are more than 3 months pregnant, as it may cause serious harm to their baby if used at that time.

Children and adolescents

The use of perindopril in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Prenessa-AS

Those who are taking, have recently taken or might take any other medicines, must consult their doctor.
Treatment with Prenessa-AS can be affected by other medicines. The doctor may need to change the dose and/or to take other precautions. These include:

- other medicines for high blood pressure, including angiotensin II receptor blockers (ARB), aliskiren or diuretics (medicines which increase the amount of urine produced by the kidneys);
- potassium-sparing drugs (e.g. triamterene, amiloride), potassium supplements or potassium-containing salt substitutes, other drugs which can increase potassium in patients’ body (such as heparin, a medicine used to thin blood to prevent clots; trimethoprim and co-trimoxazole also known as trimethoprim/sulfamethoxazole for infections caused by bacteria);
- potassium-sparing drugs used in the treatment of heart failure: eplerenone and spironolactone at doses between 12.5 mg to 50 mg per day;

- lithium for mania or depression;
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose acetylsalicylic acid, a substance presents in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting;
- medicines to treat diabetes (such as insulin or metformin);
- baclofen (used to treat muscle stiffness in diseases such as multiple sclerosis);
- medicines to treat mental disorders such as depression, anxiety, schizophrenia etc. (e.g. tricyclic antidepressants, antipsychotics);
- immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin, tacrolimus);
- trimethoprim (for the treatment of infections);
- estramustine (used in cancer therapy);
- medicines, which are most often used to treat diarrhoea (racecadotril) or avoid rejection of transplanted organs (sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTOR inhibitors);
- sacubitril/valsartan (used to treat long-term heart failure);
- allopurinol (for the treatment of gout);
- procainamide (for the treatment of an irregular heart beat);
- vasodilators including nitrates (products that make the blood vessels become wider);
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline);
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis).

Prenessa-AS with food and drink

It is preferable to take Prenessa-AS before meal.

Pregnancy and breast-feeding

If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, doctor or pharmacist should be asked for advice before taking this medicine.

Pregnancy

The doctor must be told if patients think they are (or might become) pregnant. The doctor will normally advise them to stop taking Prenessa-AS before they become pregnant or as soon as they know they are pregnant and will advise them to take another medicine instead of Prenessa-AS. Prenessa-AS 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.

Breast-feeding

The doctor must be told if patients are breast-feeding or about to start breast-feeding. Prenessa-AS is not recommended for mothers who are breast-feeding, and their doctor may choose another treatment for them if they wish to breast-feed, especially if their baby is newborn, or was born prematurely.

Driving and using machines

Prenessa-AS usually does not affect alertness but dizziness or weakness due to low blood pressure may occur in certain patients. If patients are affected in this way, their ability to drive or to operate machinery may be impaired.

How to use Prenessa-AS

This medicine must always be taken exactly as the doctor or pharmacist has told. If patients are not sure the doctor or pharmacist should be checked with.

Tablet should be swallowed with a glass of water, preferably at the same time each day, in the morning, before a meal. The doctor will decide on the correct dose for patients.

Prenessa-AS 5 mg tablets

The tablet can be divided into equal doses.

The recommended dosages are as follows:

High blood pressure

The usual starting and maintenance dose is 5 mg once daily. After one month, this can be increased to 10 mg once a day if required. 10 mg a day is the maximum recommended dose for high blood pressure.
If patients are 65 or older, the usual starting dose is 2.5 mg once a day. After a month this can be increased to 5 mg once a day and then if necessary to 10 mg once daily.

Heart failure

The usual starting dose is 2.5 mg once daily. After two weeks, this can be increased to 5 mg once a day, which is the maximum recommended dose for heart failure.

Stable coronary artery disease

The usual starting dose is 5 mg once daily. After two weeks, this can be increased to 10 mg once daily, which is the maximum recommended dose in this indication.
If patients are 65 or older, the usual starting dose is 2.5 mg once a day. After a week this can be increased to 5 mg once a day and after a further week to 10 mg once daily.

Use in children and adolescents

Use in children and adolescents is not recommended.

What to do if more Prenessa-AS was taken that it should have been?

If too many tablets are accidentally taken, patients should tell their doctor at once or contact immediately the nearest accident and emergency department. The most likely effect in case of overdose is low blood pressure which can make patients feel dizzy or faint. If this happens, lying down with the legs raised can help.

What to do if taking Prenessa-AS was forgotten?

It is important to take the medicine every day as regular treatment works better. However, if patients forget to take a dose of Prenessa-AS, they should take the next dose at the usual time. No double dose to make up for a forgotten dose can be taken.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In case of experiencing any of the following side effects that can be serious, taking Prenessa-AS should be stopped and the doctor sould be contacted immediately:
- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing (angioedema) (Uncommon – may affect up to 1 in 100 people);
- severe dizziness or fainting due to low blood pressure (Common – may affect up to 1 in 10 people);
- unusual fast or irregular heart beat, chest pain (angina) or heart attack (Very rare – may affect up to 1 in 10,000 people);
- weakness of arms or legs, or problems speaking which could be sign of a possible stroke (Very rare – may affect up to 1 in 10,000 people);
- sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing (bronchospasm) (Uncommon – may affect up to 1 in 100 people);
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell (Very rare- may affect up to 1 in 10,000 people);
- yellowing of the skin or eyes (jaundice) which could be a sign of hepatitis (Very rare – may affect up to 1 in 10,000 people);
- skin rash which often starts with red itchy patches on the face, arms or legs (erythema multiforme) (Very rare – may affect up to 1 in 10,000 people).

The doctor should be told if patients notice any of the following side effects:

Common (may affect up to 1 in 10 people)

- headache;
- dizziness;
- vertigo;

- pins and needles;
- vision disturbances;
- tinnitus (sensation of noises in the ears);
- cough;
- shortness of breath (dyspnoea);
- gastrointestinal disorders (nausea, vomiting, abdominal pain, taste disturbances, dyspepsia or difficulty of digestion, diarrhoea, constipation);
- allergic reactions (such as skin rashes, itching);
- muscle cramps;
- feeling of weakness.

Uncommon (may affect up to 1 in 100 people)

- mood swings;
- sleep disturbances;
- depression;
- dry mouth;
- intense itching or severe skin rashes;
- formation of blister clusters over the skin;
- kidney problems;
- impotence;
- sweating;
- excess of eosinophils (a type of white blood cells);
- somnolence;
- fainting;
- palpitations;
- tachycardia;
- vasculitis (inflammation of blood vessels);
- photosensitivity reaction (increased sensitivity of the skin to sun);
- arthralgia (joint pain);
- myalgia (muscle pain);
- chest pain;
- malaise;
- oedema peripheral;
- fever;
- fall;
- change in laboratory parameters: high blood level of potassium reversible on discontinuation, low level of sodium, hypoglycaemia (very low blood sugar level) in case of diabetic patients, increased blood urea, and increased blood creatinine.

Rare (may affect up to 1 in 1000 people)

- psoriasis worsening;
- changes in laboratory parameters: increased level of liver enzymes, high level of serum bilirubin;

- dark urine, feeling sick (nausea) or being sick (vomiting), muscle cramps, confusion and seizures. These may be symptoms of a condition called SIADH (inappropriate antidiuretic hormone secretion);
- decreased or absent urine output;
- flushing;
- acute renal failure.

Very rare (may affect up to 1 in 10,000 people)

- confusion;
- eosinophilic pneumonia (a rare type of pneumonia);
- rhinitis (blocked up or runny nose);
- changes in blood values such as a lower number of white and red blood cells, lower haemoglobin, lower number of blood platelets.

Frequency not known (cannot be estimated from available data)

- discoloration, numbness and pain in fingers or toes (Raynaud‘s phenomenon).

How to store Prenessa-AS

This medicine does not require any special temperature storage conditions. It should be stored in the original package in order to protect from light and kept out of the sight and reach of children.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Prenessa-AS 5 mg and 10 mg tablets. The procedure was finalised at 17 September 2021. 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, 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, con-cerned member state, CMS: Czech Republic, Estonia, Poland, Romania and Slovakia) concerned the generic versions of perindopril 5 mg and 10 mg.

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC (generic application) and there-fore contained no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence between the product and reference product.

The reference product is COVERSYL 5 mg and 10 mg film-coated tablets by Les Laboratoires Servier approved in 25 November 2004 in France.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Prenessa-AS 5 mg and 10 mg tablets from KRKA, d.d., Novo mesto.

The product is indicated for:

5 mg tablets

Hypertension:
Treatment of hypertension in adults.

Heart failure:
Treatment of symptomatic heart failure in adults.

Stable coronary artery disease:
Reduction of risk of cardiac events in adult patients with a history of myocardial infarction and/or revascularisation.

10 mg tablets:

Hypertension:
Treatment of hypertension in adults.

Stable coronary artery disease:

Reduction of risk of cardiac events in adult patients with a history of myocardial infarction and/or revascularisation.

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

II. QUALITY ASPECTS

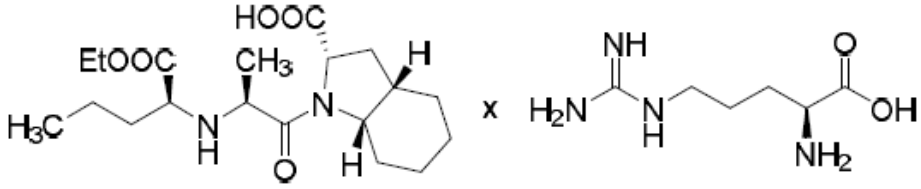
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Perindopril arginine 5 mg and 10 mg tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. generic). The products have been developed by KRKA dd., Novo mesto.
Reference products are Coversyl® 5 mg and 10 mg tablets (containing 5 mg or 10 mg perindopril arginine as active ingredient) which were the original products of Servier group.

II.2 Drug substance

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: Perindopril arginine
Systematic (IUPAC) Name: (2*S*)-2-amino-5-(diaminomethylideneamino)pentanoic acid (2*S*,3*aS*,7*aS*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3*a*,4,5,6,7,7*a*-octahydroindole-2-carboxylic acid
Structure:



The active substance is a white or almost white powder and is freely soluble in water and methanol, very slightly soluble in dichloromethane and acetonitrile. 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 and FT-IR spectra as well as X-ray powder diffraction.
The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Perindopril arginine is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance

The presented specification is in accordance with the Ph.Eur. general monograph on Substances for Pharmaceutical Use and 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.

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 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 the proposed re-test period is acceptable with no special storage condition.

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

II.3 Medicinal product

The aim was to develop tablets containing perindopril arginine as drug substance in 5 mg and 10 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product Coversyl® 5 mg and 10 mg tablets, the branded original products of Servier.
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 product is 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 product with the following appearance and composition was obtained.
5 mg strength: White or almost white capsule-shaped tablets, scored on both sides. One side of the tablet is marked with V1 - with V on one side of the score line and 1 on the other side of the score line. Tablet dimensions: approximately 8 mm x 5 mm. The tablet can be divided into equal doses.
10 mg strength: White or almost white, round, biconvex tablets marked with V2 on one side of the tablet. Diameter: approximately 8 mm.

The excipients used in the finished product are calcium chloride hexahydrate, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.
All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has 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 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 Aluminium- OPA/Alu/PVC. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with no special storage conditions 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 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.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of perindopril are well known. As perindopril is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Pharmacology

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme – ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone.
No new non-clinical studies were conducted by the applicant and no such studies were required.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant and no such studies were required.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable.

III.5 Ecotoxicology/environmnetal risk assessment (ERA)

Since Prenessa-AS 5 mg and 10 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion onthe non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of the active substance are well-known. No new nonclinical studies were needed. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and there was no objections to approval of Prenessa-AS 5 mg and 10 mg tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamics, pharmacokinetics, efficacy and safety of the active substance are well established. The clinical overview refers to literature publications. Furthermore to support the application, the applicant has submitted the report of one pivotal bioequivalence study.

IV.2 Pharmacokinetics

Absorption
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 prodrug. 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 arginine should be administered orally in a single daily dose in the morning before a meal.
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Distribution
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.

Elimination
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.

Bioequivalence study

To support the application, it was submitted as report one pivotal single-dose bioequivalence study (19-657) with the strength of 10 mg tablets.

By the Sponsor's statement the study was conducted in compliance with the ICH GCP, EMA guidelines and the current version of the Declaration of Helsinki (Brazil, October 2013).

Study No. 19-657 was a randomized, open label, two treatment, two period, two sequence, single dose, crossover bioequivalence study of test product Perindopril 10 mg tablets and reference product Bioprexanil® 10 mg film-coated tablets in healthy, adult, non-smoking, male subjects under fasting conditions. A washout period of at least 7 days was kept between each consecutive dosing period. Chosen wash-out period was long enough to avoid any carry-over effect. 44 volunteers were enrolled, 43 of them completed the study. 43 subjects were included

in the final statistical analysis of AUC_{0-t} and C_{max}.
Test and Reference products contains 10 mg perindopril (as perindopril arginine).

Test and Reference products in study No. 19-657:

- Test: Perindopril 10 mg tablets, manufacturer: Krka, d. d., Novo mesto, Slovenia, EU, Batch number: R44248
- Reference: Bioprexanil® 10 mg film-coated tablets, MAH: Servier Pharma d.o.o., Slovenia, manufacturer: Anpharm Przedsiebiorstwo Farmaceutyczne S.A., Poland, EU, Batch number: 335588

After an overnight fast of at least 10.00 hrs a single oral dose of either the test product or the reference product was administered as per randomization schedule in each study period with 240 ± 5 mL of room temperature bottled water.

A total of 15 blood samples (5ml each) were collected from the subjects in K_2EDTA vacutainers during each study period at pre-dose (collected within 60 minutes prior to dosing), 0.167, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, and 6 hrs post-dose.

Analyzed compound:
A validated LC-MS/MS analytical method was used for the determination of perindopril from the human plasma samples.

Pharmacokinetic Variables:
- Primary variables: C_{max} and AUC_{0-t}, AUC_{0-inf}
- Secondary variable: AUC_{0-t} /AUC_{0-inf}, t_{max}, K_{el} and $t_{1/2}$

Criteria for Bioequivalence:
The 90% CI of the relative mean plasma perindopril AUC_t and C_{max} of the test to reference product should be between 80.00 and 125.00%.

Results:

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	95.50 ±30.82	96.62 ±31.15	79.02 ±23.80	0.75 (0.50-1.33)
Reference	91.24 ± 26.03	92.28 ±26.25	79.42 ±22.37	0.75 (0.50-1.67)
***Ratio (90% CI)**	103.90% (101.13%-106.74%)	103.91% (101.19%-106.69%)	98.88% (91.73% - 106.59%)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Safety:

A total of nine adverse events were reported during the clinical phase of the study. All the AEs were assessed as treatment related (probably related to the investigational medicinal product). All AEs were mild in severity and all resolved without intervention prior to the end of the study. The AE with the highest incidence was headache (4 events reported by 3 subjects).

Pharmacokinetic conclusion:

Based on the submitted bioequivalence studies Test Product (Perindopril 10 mg tablets, manufacturer: Krka, d. d., Novo mesto, Slovenia, EU) is considered bioequivalent with Reference Product (Bioprexanil® 10 mg film-coated tablets, manufacturer: Anpharm Przedsiebiorstwo Farmaceutyczne S.A., Poland, EU).

Biowaiver

Perindopril tablets are available in 5 mg and 10 mg strengths. For additional strength of 5 mg a biowaiver is claimed based on the justification below.
Both strengths are manufactured by the same manufacturing process. The qualitative composition of both strengths is the same and the composition of the strengths is quantitatively proportional. According SmPC of the Reference product “It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.” *In vitro* dissolution profiles between Krka's 5 mg and 10 mg strengths are comparable.
Thus the general requirements of biowaiver were demonstrated.

IV.3 Pharmacodynamics

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases with no effect on heart rate.
Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours; trough effects are about 87 % to 100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.
Discontinuation of treatment does not lead to a rebound effect.
Perindopril reduces left ventricular hypertrophy.
In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media/lumen ratio of small arteries.

An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.
Perindopril reduces cardiac work by a decrease in pre-load and after-load.
Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.
In comparative studies, the first administration of 2.5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

IV.4 Clinical efficacy

Clinical efficacy of perindopril is well-established. No new efficacy study was performed which is acceptable for this type of application. The Applicant has provided an adequate literature review.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.
The Applicant has provided an adequate literature review.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Prenessa-AS 5 mg and 10 mg tablets.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Prenessa-AS 5 mg and 10 mg tablets.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product and for this type of applications the bioequivalence studies are pivotal. The Applicant has adequately demonstrated bioequivalence between test product Perindopril 10 mg tablets (as perindopril arginine) and the reference product Bioprexanil 10 mg film-coated tablets.

The application contains an adequate review of published clinical data.

The application concerns a generic product.

The products is indicated for:

5 mg tablets

Hypertension:
Treatment of hypertension in adults.

Heart failure:
Treatment of symptomatic heart failure in adults.

Stable coronary artery disease:
Reduction of risk of cardiac events in adult patients with a history of myocardial infarction and/or revascularisation.

10 mg tablets:

Hypertension:
Treatment of hypertension in adults.

Stable coronary artery disease:
Reduction of risk of cardiac events in adult patients with a history of myocardial infarction and/or revascularisation.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Prenessa-AS 5 mg and 10 mg tablets. The applicant and the future holder of authorisation is Krka, d.d., Novo mesto.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator product was COVERSYL 5 mg, 10 mg film-coated tablets by Les Laboratoires Servier authorised for marketing since 25 November 2004 in the France.

The products is indicated for:

5 mg tablets

Hypertension:
Treatment of hypertension in adults.

Heart failure:
Treatment of symptomatic heart failure in adults.

Stable coronary artery disease:
Reduction of risk of cardiac events in adult patients with a history of myocardial infarction and/or revascularisation.

10 mg tablets:

Hypertension:
Treatment of hypertension in adults.

Stable coronary artery disease:
Reduction of risk of cardiac events in adult patients with a history of myocardial infarction and/or revascularisation.

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 Prenessa-AS 5 mg and 10 mg tablets from Krka, d.d., Novo mesto.

V.2 Classification

Prescription only

V.3 Package Leaflet and user consultation

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 English.

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