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# Public Assessment Report

**Name of the Product:**

# Losartan/Amlodipine Krka

## 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets

## (losartan potassium/amlodipine besilate)

**Procedure number: HU/H/0375/001-004/DC**

**Marketing authorisation holder: Krka d.d.**

**Date: 13 June 2016**

**CONTENT**

# LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Losartan/Amlodipine Krka (in the Czech Republic Tenloris, in Germany Losamlo) 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets. The holder of the marketing authorisation is Krka, d.d. in the reference member state.

The active substances are losartan potassium and amlodipine besilate.

Each 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg combionation film-coated tablets contain 50 mg losartan potassium and 6.94 mg amlodipine besilate (equivalent to 5 mg amlodipine), or 50 mg losartan potassium and 13.88 mg amlodipine besilate (equivalent to 10 mg amlodipine), or 100 mg losartan potassium and 6.94 mg amlodipine besilate (equivalent to 5 mg amlodipine), or 100 mg losartan potassium and 13.88 mg amlodipine besilate (equivalent to 10 mg amlodipine), respectively.

The other ingredients (excipients) are:
- in the tablet: lactose monohydrate; cellulose, powdered (E460); starch, pregelatinised; maize starch; cellulose, microcrystalline (E460); silica, colloidal anhydrous; magnesium stearate (E572); sodium starch glycolate (type A) and iron oxide yellow (E172);
- in the film coating:
    - the 50 mg/5 mg film-coated tablets: iron oxide red (E172); iron oxide yellow (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b);
    - the 50 mg/10 mg film-coated tablets: iron oxide red (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b);
    - the 100 mg/5 mg film-coated tablets: iron oxide red (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b);
    - the 100 mg/10 mg film-coated tablets: iron oxide yellow (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b).

The 50 mg/5 mg film-coated tablets are brownish orange, oval (15 mm x 7 mm), slightly biconvex.
The 50 mg/10 mg film-coated tablets are red-brown, oval (15 mm x 7 mm), slightly biconvex.
The 100 mg/5 mg film-coated tablets are pink, oval (18 mm x 9 mm), biconvex.
The 100 mg/10 mg film-coated tablets are pale brownish yellow, oval (18 mm x 9 mm), biconvex.

The products as film-coated tablets in blisters in boxes.

Losartan/Amlodipine Krka film-coated tablets (Further on: Losartan Amlodipine Krka) contain two active substances. Both of these substances help to control high blood pressure.

- Losartan belongs to a group of medicines called “angiotensin-II receptor antagonists” which lower blood pressure by relaxing the blood vessels.
- Amlodipine belongs to a group of substances called “calcium channel blockers”. Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening thereby also reducing blood pressure.

The actions of both these substances contribute to stopping the tightening of blood vessels, so that blood vessels relax and blood pressure decreases.

Losartan/Amlodipine Krka is used for the treatment of high blood pressure (hypertension) in patients who are already taking losartan and amlodipine at these doses, instead of taking two medicines separately.

**What patients need to know before taking Losartan/Amlodipine Krka**

*Those who*
- are allergic to losartan, amlodipine, or any of the other ingredients of this medicine, or to any other calcium antagonist. This may be itching, reddening of the skin or difficulty in breathing;
- have severe low blood pressure (hypotension);
- have narrowing of the aortic heart valve (aortic stenosis) or shock (including cardiogenic shock, a condition where the heart is unable to supply enough blood to the body;
- suffer from heart failure after a heart attack;
- are more than 3 months pregnant. (It is also better to avoid Losartan/Amlodipine Krka in early pregnancy);
- have a severely impaired liver function;
- have diabetes or impaired kidney function and are taking a medicine called aliskiren to reduce blood pressure.

*must not take Losartan/Amlodipine Krka.*

*Warnings and precautions*

Patients must tell their doctor if they think they are (or might become) pregnant. Losartan/Amlodipine Krka is not recommended in early pregnancy, and must not be taken if the patient is more than 3 months pregnant, as it may cause serious harm to the baby if used at that stage.

It is important to inform the doctor before taking Losartan/Amlodipine Krka if the patient
- has had a history of angiooedema (swelling of the face, lips, throat, and/or tongue);
- suffers from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in the body,
- receives diuretics (medicines that increase the amount of water that passes out through the kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in the body;

- is known to have narrowing or blockage of the blood vessels leading to the kidneys or if the patient have received a kidney transplant recently;
- the liver function is impaired;
- suffers from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias. Special caution is necessary when the patient is treated with a ß-blocker concomitantly;
- has problems with the heart valves or heart muscle;
- suffers from coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) or from cerebrovascular disease (caused by a reduced blood circulation in the brain);
- suffers from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland);
- has had a recent heart attack;
- has or has had a severe increase in blood pressure (hypertensive crisis);
- is elderly and the dose needs to be increased;
- is taking a medicine called aliskiren to reduce blood pressure.

*Children and adolescents*

The use of Losartan/Amlodipine Krka in children and adolescents up to the age of 18 years is not recommended.

*Other medicines and Losartan/Amlodipine Krka*

It is advisable to inform the doctor if the patient is taking, have recently taken or might take any other medicines.

It is particularly important if the patient is taking the following medicines while under treatment with Losartan/Amlodipine Krka:
- other blood pressure lowering medicines as they may additionally reduce the blood pressure. Blood pressure may also be lowered by one of the following drugs / class of drugs: tricyclic antidepressants, antipsychotics, baclofene, amifostine;
- medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamteren, spironolactone] or heparin);
- non-steroidal anti-inflammatory drugs such as indomethacin, including COX-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain) as they may reduce the blood pressure lowering effect of losartan.

If the kidney function is impaired, the concomitant use of these medicines may lead to a worsening of the kidney function.

Losartan/Amlodipine Krka may affect or be affected also by other medicines, such as:
- ketoconazole, itraconazole, fluconazole (anti-fungal medicines),
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV),

- rifampicin, erythromycin, clarithromycin (antibiotics),
- preparations of St. John's Wort (*Hypericum perforatum*),
- verapamil, diltiazem (heart medicines),
- dantrolene (infusion for severe body temperature abnormalities),
- simvastatin (a cholesterol lowering medicine).

Lithium containing medicines should not be taken in combination with Losartan/Amlodipine Krka without close supervision by the doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

*Losartan/Amlodipine Krka with food and drink*

Grapefruit juice and grapefruit should not be consumed by people who are taking Losartan/Amlodipine Krka. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Losartan/Amlodipine Krka.

*Pregnancy and breast-feeding*

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

In case when the patient thinks she is (or might become) pregnant, the doctor will normally advise her to stop taking Losartan/Amlodipine Krka before she becomes pregnant or as soon as she know she is pregnant and will advise her to take another medicine instead of Losartan/Amlodipine Krka. This medicine is not recommended in early pregnancy, and must not be taken when the patient is more than 3 months pregnant, as it may cause serious harm to the baby if used after the third month of pregnancy.

Losartan/Amlodipine Krka 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 the baby is a new-born, or born prematurely.

*Driving and using machines*

Losartan/Amlodipine Krka may affect the ability to drive or use machines. If the tablets make the patient feel sick, dizzy or tired, or causes a headache, it is better not to drive or use machines and the doctor should be contacted immediately.

*Losartan/Amlodipine Krka contains lactose*

Those who have been told by their doctor that they have an intolerance to some sugars, contact their doctor before taking this medicinal product.

**How to take Losartan/Amlodipine Krka?**

The recommended dose of Losartan/Amlodipine Krka is one tablet per day.

The tablets should be swallowed with a glass of water, with or without food. Patients are advised trying to take the daily dose at about the same time each day. Losartan/Amlodipine Krka must not be taken with grapefruit juice.

It is important that the patient continues to take Losartan/Amlodipine Krka until the doctor tells otherwise.

*Use in children and adolescents*

The use of Losartan/Amlodipine Krka in children and adolescents is not recommended.

*What to do if more Losartan/Amlodipine Krka has been taken than it should?*

If a patient accidentally takes too many tablets, the doctor must be contacted immediately. Taking too many tablets may cause the blood pressure to become low or even dangerously low. The patient may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. The skin could feel cool and clammy and the patient could lose consciousness.

*What to do if taking Losartan/Amlodipine Krka has been forgotten?*

If the patient accidentally misses a daily dose, the next dose should be taken as normal. Double dose should not be taken to make up for a forgotten dose.

*May taking Losartan/Amlodipine Krka be stopped?*

The doctor will advise the patient how long to take this medicine. Your condition may return if you stop using your medicine before you are advised.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**Possible side effects**

Like all medicines, Losartan/Amlodipine Krka can cause side effects, although not everybody experiences them.

If experiencing any of the following, severe side effects after taking this medicine the doctor must be visited immediately:
- sudden wheeziness, chest pain, shortness of breath or difficulty in breathing;
- swelling of eyelids, face or lips;
- swelling of the tongue and throat which causes great difficulty breathing;

- severe skin reactions including intense skin rash, hives, reddening of the skin over the whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions;
- heart attack, abnormal heart beat;
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell.

*Side-effects due to amlodipine*

The following *common* (that may affect up to 1 in 10 people) side-effects have been reported. If any of these cause problems or if they last for more than one week, the doctor should be contacted:
- headache, dizziness, sleepiness (especially at the beginning of treatment),
- palpitations (awareness of your heart beat), flushing,
- abdominal pain, feeling sick (nausea),
- ankle swelling (oedema), tiredness,

Other side-effects that have been reported include the following list. If any of these get serious, the doctor should be informed.

*Uncommon* **(**may affect up to 1 in 100 people):
- mood changes, anxiety, depression, sleeplessness,
- trembling, taste abnormalities, fainting, weakness,
- numbness or tingling sensation in your limbs; loss of pain sensation,
- visual disturbances, double vision, ringing in the ears,
- low blood pressure,
- sneezing/running nose caused by inflammation of the lining of the nose (rhinitis),
- altered bowel habits, diarrhoea, constipation, indigestion, dry mouth, vomiting (being sick),
- hair loss, increased sweating, itchy skin, red patches on skin, skin discoloration,
- disorder in passing urine, increased need to urinate at night, increased number of times of passing urine,
- inability to obtain an erection, discomfort or enlargement of the breasts in men,
- weakness, pain, feeling unwell,
- joint or muscle pain, muscle cramps, back pain,
- weight increase or decrease,
- chest pain.

*Rare* (may affect up to 1 in 1,000 people): confusion.

*Very rare* **(**may affect up to 1 in 10,000 people):
- decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage),
- excess sugar in blood (hyperglycaemia),
- a disorder of the nerves which can cause weakness, tingling or numbness,

- cough,
- swelling of the gums,
- abdominal bloating (gastritis),
- abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests,
- increased muscle tension,
- inflammation of blood vessels, often with skin rash,
- sensitivity to light,
- disorders combining rigidity, tremor, and/or movement disorders.

*Side-effects due to losartan*

*Common* (may affect up to 1 in 10 people):
- dizziness,
- low blood pressure (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under treatment with high dose diuretics),
- dose-related orthostatic effects such as lowering of blood pressure appearing when rising from a lying or sitting position,
- debility,
- fatigue,
- too less sugar in the blood (hypoglycaemia),
- too much potassium in the blood (hyperkalaemia),
- changes in kidney function including kidney failure,
- reduced number of red blood cells (anaemia),
- increase in blood urea, serum creatinine and serum potassium in patients with heart failure.

*Uncommon* (may affect up to 1 in 100 people):
- somnolence,
- headache,
- sleep disorders,
- feeling of increased heart rate (palpitations),
- severe chest pain (angina pectoris),
- shortness of breath (dyspnoea),
- abdominal pain,
- obstipation,
- diarrhoea,
- nausea,
- vomiting,
- hives (urticaria),
- itching (pruritus),
- rash,
- localised swelling (oedema),
- cough.

*Rare* (may affect up to 1 in 1,000 people):
- hypersensitivity,
- angiooedema,
- inflammation of blood vessels (vasculitis including Henoch-Schönlein purpura),
- numbness or tingling sensation (paraesthesia),
- fainting (syncope),
- very rapid and irregular heartbeat (atrial fibrillation),
- brain attack (stroke),
- inflammation of the liver (hepatitis),
- elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.

*Not known* (frequency cannot be estimated from the available data):
- reduced number of thrombocytes,
- migraine,
- liver function abnormalities,
- muscle and joint pain,
- flu-like symptoms,
- back pain and urinary track infection,
- increased sensitivity to the sun (photosensitivity),
- unexplained muscle pain with dark (tea-colored) urine (rhabdomyolysis),
- impotence,
- inflammation of the pancreas (pancreatitis),
- low levels of sodium in the blood (hyponatraemia),
- depression,
- generally feeling unwell (malaise),
- ringing, buzzing, roaring, or clicking in the ears (tinnitus),
- disturbed taste (dysgeusia).

**How to store Losartan/Amlodipine Krka?**

This medicinal product does not require any special storage conditions but it should be kept out of the sight and reach of children.

# Scientific discussion

## during the initial phase

**This module reflects the scientific discussion for the approval of Losartan/Amlodipine Krka 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets. The procedure was finalised at 27 April 2016. 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, concerned member states, CMS: the Czech Republic, Germany and Slovenia) concerned the generic version of losartan/amlodipine fix combinations 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets (Losartan/Amlodipine Krka, named Tenloris in the Czech Republic and Losemlo in Germany).

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Losartan/Amlodipine Krka 50/5 mg, 50/10 mg, 100/5 mg, 100/10 mg film-coated tablets from Krka d.d., Novo mesto.

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

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

The marketing authorisation has been granted pursuant to Article 10(b) of Directive 2001/83/EC (fixed combination). The applicant has adequately demonstrated bioequivalence between the combination and co-administered monocomponent reference products.

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 and increased compliance. Combining a dihydropyridine calcium channel blocker (CCB, e.g. amlodipine) and an angiotensin II receptor antagonist (AIIRA, e.g. losartan) has the benefit of reducing blood pressure via different mechanisms of action that results in additive blood pressure reduction. CCBs and AIIRAs have complementary mechanism of action. The vasodilatory effects of CCBs cause an activation of the renin-angiotensin-aldosterone system (RAAS), which is antagonized by an AIIRA. AIIRAs are particularly effective in patients with high renin levels, whereas CCBs are effective in low-renin patients, which may result in increasing efficacy across a wider spectrum of patients.

# II. QUALITY ASPECTS

## II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Losar-tan/Amlodipine Krka 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets via a decentralized procedure according to Article 10b of consolidated Directive 2001/83/EC (i.e. a fixed combination application). The products have been developed by Krka d.d., Novo mesto.

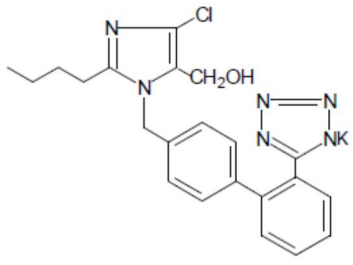
The reference products used were Lorzaar® Protect 100 mg film-coated tablets (Merck Sharp & Dohme Ltd.) and Istin$^{TM}$ 10 mg tablets (Pfizer) which are monocomponent formulations of losartan potassium and amlodipine besilate, respectively.

## II.2 Drug substances

### *II.2.1 Losartan potassium*

For the active substance losartan potassium two European Pharmacopoeia (Ph. Eur.) certificates of suitability (CEPs) have been submitted.
Data on the quality and manufacture of the active substance were provided in the submission using the CEP procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

Ph. Eur. name: losartan potassium
Chemical name: 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-imidazole-5-methanol, potassium salt
Structure:




The active substance is white, odourless crystalline powder, hygroscopic; freely soluble in water, methanol, ethanol, and slightly soluble in 0.1 M hydrochloric acid. It shows polymorphism, the manufacturers consistently produce the same polymorphic form.

The CEP holders presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure, impurity profile of the substance containing detailed information about genotoxic impurities, residual solvents and catalysts has been assessed during the CEP procedures.

The active substance is official in the Ph. Eur. Additional specifications have been set for the active substance on the CEPs and by the drug product manufacturer, which include the following tests: appearance, solubility, identification of losartan by IR, identification of potassium by chemical reaction, heavy metals, loss on drying, related substances, residual solvents, assay and microbiological purity.

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

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

The substance complies with the requirements of the 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.

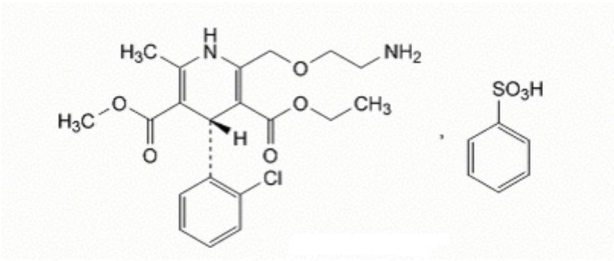
Stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 3 years is acceptable when stored at 25°C in the prescribed packaging material.

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

### *II.2.2 Amlodipine besilate*

For the active substance amlodipine besilate a CEP has been submitted. Data on the quality and manufacture of the active substance was provided in the submission using CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

Ph. Eur. name: amlodipine besilate
Chemical name: 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate
Structure:




and enantiomer

The drug substance is white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol. Its anhydrous crystalline form has been confirmed.

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

Evidence of the structure, impurity profile of the drug substance containing detailed information about genotoxic impurities, residual solvents and catalysts has been assessed during the CEP procedure.

The active substance is official in the Ph. Eur., additional specifications have been set on the CEP and by the drug product manufacturer, which includes the following tests: appearance, solubility, identification by IR, optical rotation, related substances, water content, sulphated ash, residual solvents, assay, particle size distribution and microbiological purity.

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 detail in the Ph. Eur. 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.

A retest period of 60 months and the packaging material (double polyethylene bags /outer black/ placed in a fibre board drum) have been mentioned on the CEP.

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

## II.3 Medicinal product

The aim was to develop fixed dose combinations of losartan potassium/amlodipine besilate film-coated tablets 50 mg/5 mg, 50 mg/10 mg 100 mg/5 mg and 100 mg/10 mg for oral administration, which would be equivalent to the combinations of reference products Lorzaar® Protect film-coated tablets and Istin™ tablets in terms of bioavailability and stability properties.

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 impurity profile the product is shown to be similar to the reference product.

Based on the comparative dissolution profiles of both active substances, the test products could not be considered *in-vitro* equivalent to the reference products (comparison using the similarity factors $f_2$). However, since the *in-vivo* bioequivalence study prevails over the *in vitro* dissolution study, the lack of *in vitro* equalivalence does not affect the efficacy, quality and safety of the 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 products with the following appearance have been developed:

- 50 mg/5 mg film-coated tablets are brownish orange, oval (15 mm x 7 mm), slightly biconvex;
- 50 mg/10 mg film-coated tablets are red-brown, oval (15 mm x 7 mm), slightly biconvex;
- 100 mg/5 mg film-coated tablets are pink, oval (18 mm x 9 mm), biconvex;
- 100 mg/10 mg: the film-coated tablets are pale brownish yellow, oval (18 mm x 9 mm), biconvex.

The excipients used in the finished products are:

- tablet core: lactose monohydrate; cellulose, powdered; starch, pregelatinised; maize starch; cellulose, microcrystalline; silica, colloidal anhydrous; magnesium stearate; sodium starch glycolate (type A) and iron oxide yellow;
- film coating: poly(vinyl alcohol) ; titanium dioxide; macrogol 3000; talc and iron oxide red (in the 50 mg/5 mg, 50 mg/10 mg and 100 mg/5 mg film-coated tablets), iron oxide yellow (in the 50 mg/5 mg and 100 mg/10 mg film-coated tablets).

All excipients, except Opadry film-coating agent and iron oxides comply with respective Ph. Eur. monograph. Yellow and red iron oxides comply with USP/NF and E172. Opadry 85F28751 II HP White is controlled according to an in-house specification.

Compliance of the product with the general monograph of the Ph. Eur. on *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 blister packs of cold formed OPA/Al/PVC foil and aluminium foil. Specifications and quality certificates for all packaging components are enclosed.

The stability testing is performed according to a reduced stability testing protocol (matrixing) following *Note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products* (CPMP/ICH/4101/00, February 2002), or ICH Q1D. Based on the qualitative composition of the products, reduced testing by matrixing is acceptable.

Based on the results, a shelf-life of 24 months with no special storage conditions is approved.

The SmPC, Patient Information (Package) Leaflet and label texts are pharmaceutically acceptable.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their 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 products are approvable.

# III. NON-CLINICAL ASPECTS

## III.1 Introduction

The pharmaco-toxicological properties of losartan 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 losartan and amlodipine.

## III.2 Pharmacology

Losartan is an angiotensin-II receptor (type $AT_1$) antagonist and amlodipine is a dihydro-pyridine calcium channel blocker. Both active substances are well-known compounds. No further information was provided regarding the pharmacology of losartan and amlodipine.

## III.3 Pharmacokinetics

Pharmacokinetic studies performed in animals with the combination of losartan/amlodipine were not found in available literature by the applicant. There are only data on losartan and amlodipine alone.

In addition no new non-clinical pharmacokinetic studies were conducted by the applicant.

## III.4 Toxicology

Published information on toxicological studies with losartan and amlodipine was the basis for the evaluation.

Toxicity studies showed that amlodipine is moderately toxic after oral application to laboratory animals. Toxic effects on kidneys were seen in repeated dose studies with high dosages of amlodipine. Toxicity studies indicated relative low toxicity of losartan.

The safety of Losartan/Amlodipine Krka film-coated tablets was additionally evaluated with single and repeat-dose toxicity study on mice and rats in comparison with the combination of the monocomponent reference drugs. The study demonstrated that acute and subacute toxicity parameters of fixed dose combination of amlodipine + losartan are not different from those of combination of monocomponents.

## III.5 Ecotoxicity/environmental risk assessment

The combination products are indicated for a substitution indication and will replace the use of the co-administered single products, consequently, this will not lead to an increased environmental exposure.

In addition to this justification, the applicant presented an environmental risk assessment report performed separately for each compound within the product in accordance to the *Guideline on the environmental risk assessment of medicinal products for human use* (EMEA/CHMP/SWP/4447/00) and *Questions and answers on "Guideline on the environmental risk assessment of medicinal products for human use"* (EMA/CHMP/SWP/44609/2010).

The presented environmental risk assessment demonstrated that Losartan/Amlodipine Krka film- coated tablets do not represent any risk for the environment if used according to the proposed SmPC.

## III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of losartan 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 is primarily related to the benefits of fixed combination therapy in terms of simplification of the therapeutic regimen and increased compliance.

The applicant conducted a bioequivalence study and a pharmacokinetic interaction study.

## IV.2 Pharmacokinetics

### *IV.2.1 Bioequivalence study*

To support the application, the applicant submitted a bioequivalence study report. The bioequivalence study was carried out with the 100 mg/10 mg strength.

*Biowaiver*

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

a) the pharmaceutical products are manufactured by the same manufacturing process;
b) the qualitative composition is the same for all four strengths except for colouring agent ferric oxide in the film-coating, which is used to differentiate between different strengths;
c) the cores of the film-coated tablets consist of two layers, i.e. one layer includes losartan potassium and another layer includes amlodipine besilate; quantitative composition of the strengths fulfils requirements for proportionality.
d) in vitro dissolution testing at the required pH values have shown similarity of dissolution profiles.

Dose-independent pharmacokinetics in the therapeutic range has also been demonstrated by the applicant.

*Bioequivalence study design chosen and main objective of the study*

The clinical development performed by the applicant comprised of a comparative, single-dose, two-way, cross-over bioavailability study, during which the subjects received the fixed dose combination of losartan/amlodipine 100mg/10 mg film-coated tablets as test treatment (T) versus concomitant application of one Istin$^{TM}$ 10 mg tablet (Pfizer

Manufacturing Deutschland GmbH) and one Lorzaar® Protect 100 mg film-coated tablet (Merck Sharp & Dohme Ltd., UK) as reference treatment (R) to healthy male volunteers under fasting conditions.

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

The subjects were randomized and dosed.

Determination of both amlodipine and losartan in plasma samples was performed using validated LC/MS/MS.

Pharmacokinetic parameters $AUC_i$, $AUC_t$, $R_{AUC}$ (residual area), $C_{max}$, $T_{max}$, $K_{el}$ and $T_{half}$ for losartan and $AUC_{0-72h}$, $C_{max}$ and $T_{max}$ for amlodipine were determined on the basis of individual concentrations.

The comparison of test and reference products was performed by the bioequivalence guideline in force during the evaluation. Confidence intervals were determined for the ln transformed $AUC_i$, $AUC_t$, and $C_{max}$ parameters of losartan and $AUC_{0-72h}$ and $C_{max}$ parameters of amlodipine using the formulations least squares means (LS-Means) and the residual values obtained from ANOVA. For the $T_{max}$ parameter the nonparametric test was applied.

Bioequivalence was concluded if the 90% confidence intervals for the ratio of the means of $C_{max}$ and $AUC_t$ parameters of losartan and $AUC_{0-72h}$ and $C_{max}$ parameters of amlodipine were included within interval 80.00-125.00%.

*Summary of results of BE study*

90% Confidence Intervals of ratio of LS-Means (T/R) losartan in plasma

| Parameter | Lower Limit | Ratio | Upper Limit |
|---|---|---|---|
| $AUC_t$ | 94,37% | 97,60% | 100,94% |
| $C_{max}$ | 98,20% | 106,81% | 116,16% |

90% Confidence Intervals of ratio of LS-Means (T/R) amlodipine in plasma

| Parameter | Lower Limit | Ratio | Upper Limit |
|---|---|---|---|
| $AUC_{0-72h}$ | 94,84% | 97,02% | 99,24% |
| $C_{max}$ | 91,51% | 94,04% | 96,64% |

$AUC_i$: Area under the plasma concentration-time curve from time 0 to infinity
$AUC_t$: Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
$C_{max}$: Peak plasma concentration

Based on the results, losartan/amlodipine 100 mg/10mg KRKA film-coated tablets formulation, which was tested in comparison with co-administration of Istin™ 10 mg tablets (amlodipine, Pfizer Manufacturing Deutschland GmbH, Germany, EU) and one Lorzaar® Protect 100 mg film-coated tablets (losartan, MERCK Sharp & Dohme Ltd., UK, EU) (comparative treatment) administered simultaneously are bioequivalent under fasting condition.

*Conclusion on the bioequivalence study*

The results of bioequivalence study with losartan/amlodipine 100 mg/10mg strength can be extrapolated to other strengths: 100mg/5mg, 50mg/10mg and 50mg/5mg according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

***IV.2.2 Pharmacokinetic interaction study***

Additionally an open label, two cohort, randomized, pharmacokinetic interaction study has been conducted in healthy male volunteers in order to investigate the potential impact of multiple doses of amlodipine on losartan, and metabolite E-3174 bioavailability and *vice versa* following the administration of losartan (Cozaar® 100 mg film-coated tablets) and amlodipine (Norvasc® 10 mg tablets), after oral administration, each separately versus the co-administration.

Another objective was the assessment of safety following administration of study treatment and comparison of tolerability profiles (CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010).

Based on the results of this interaction study, and using data from relevant literature, it can be concluded that the interaction effect when amlodipine and losartan are administered alone or in combination with each other are not clinically significant. Considering the evident efficacy and safety of losartan/amlodipine combination in the proposed doses (100/10 mg), the detected pharmacokinetic interactions do not influence the efficacy or safety of combined losartan and amlodipine use.

## IV.3 Pharmacodynamics

Combining a CCB with an AIIRA has the benefit of reducing BP via different mechanism of action that results in additive BP reductions. This has been also evident in several clinical trials where fixed dose combination losartan (L) + amlodipine (A) were investigated. Furthermore, some of this trial demonstrated significant and rapid BP reductions of the fixed dose combination L+A. AIIRA increase both arterial and venous dilatation, which can counteract CCB-in-

duced preferential arterial dilatation by reducing pressure gradients between arteriolar and venular capillaries. Thus, AIIRAs are likely to reduce the incidence of lower extremity oedema associated with use of CCB.

The CCB is effective in low-renin hypertension and the AIIRA in high-renin hypertension, which is of tremendous importance in a today's more personalised treatment algorithm that incorporates varying pathophysiologies of hypertension. As low-renin hypertension constitutes approx. one third of all hypertensives and the other third are medium/high renin hypertensive patients, combining both classes could improve the success of treatment across a wider spectrum of patients. Both drugs have generally neutral effects on metabolic parameters such as blood lipid levels and insulin sensitivity and can be administered to nearly all hypertensive patients.

## IV.4 Clinical efficacy

Treatment guidelines suggest that the combination of an AIIRA and a CCB provides an effective option for patients with hypertension. Considering the important role of the renin-angiotensin-aldosterone system in the pathophysiology of hypertension, a key component of combination therapy should include a RAAS inhibitor. The AIIRA based combinations have the added advantage of good tolerability, with the AIIRA potentially reducing peripheral oedema that may be associated with amlodipine. In particular, RAAS inhibitor-based treatments are the preferred option for high-risk hypertensive patients with diabetes, metabolic syndrome, or kidney disease. Some publications suggest that a CCB/RAAS blocker combination could be a useful option.

The fixed-dose combination (FDC) of losartan (L)+amlodipine(A) has been investigated in several clinical trials. These trials were mostly randomised, multicentre and double-blind trials, some of them compared the FDC to either amlodipine monotherapy, losartan monotherapy or both of them. One trial was a factorial phase II study, in which all the proposed strengths have been investigated.

Based on IMS market expertise, losartan and amlodipine have been adequately co-prescribed. There is evidence of established use of the combination supporting the applicant's claim.

Regarding the efficacy profile the proposed substitution indication is acceptable.

## IV.5 Clinical safety

*Monocomponents alone*

Amlodipine and losartan are well known substances which have both been widely used in clinical practice for several years. Their safety profile are well known, and both drugs are well tolerated when administered as monotherapy.

*Losartan/amlodipine combination*

In a double blind multicentre study, where efficacy of FDC losartan 50 mg + amlodipine 5 mg or losartan 50 mg + amlodipine 10 mg were compared to amlodipine 5 mg or 10 mg in patients with stage 2 hypertension, also a safety evaluation has been done. For the safety analysis, 73 subjects were included in losartan + amlodipine group and 75 amlodipine monotherapy group. A total of 86 treatment emergent adverse events (TEAE) were reported in 47 subjects (44 in 23 subjects (31.5%) in the losartan + amlodipine combination group and 42 in 24 subjects (32.0%) in the amlodipine monotherapy group.)

The most frequently reported treatment related adverse events included dizziness, headache, somnolence, hot flush, and peripheral oedema. No deaths were reported during this trial.

In a study where losartan + amlodipine fixed dose combination and amlodipine 10 mg monotherapy were compared in hypertensive patients who respond poorly to amlodipine 5 mg monotherapy, a safety evaluation has been done on 184 patients. The major adverse event related to the treatment drugs was headache, with similar rates of occurrence between the 2 groups. In the monotherapy therapy group two patients discontinued due to AE. Overall the FDC exhibited a safety profile generally comparable to amlodipine 10 mg monotherapy. Furthermore, in FDC group there were no reports about peripheral oedema (in monotherapy group 1 report), which supports the notion that combining an AIIRA with a CCB reduces the incidence of CCB-induced oedema.

A safety analysis in randomized, phase II, double-blind study which evaluated dose response relationship of the fixed dose combination losartan 50 + amlodipine 5, losartan 100 + amlodipine5, losartan 50 + amlodipine10, losartan 100 + amlodipine 10 and monotherapies amlodipine (5 mg or 10 mg) and losartan (50 mg or 100 mg) demonstrated that the incidence of adverse events was not significantly different between treatment groups. The majority of AE were reported as mild to moderate (>95 %) and included dizziness, headache, chest discomfort and reflux esophagitis. There were no reports of serious AE in any of the combination therapy groups. There were no deaths during the study and no clinically meaningful differences among the treatment groups in laboratory test, no statistically significant differences in pulse rate, physical examination or ECG. The study showed that tolerability of these fixed doses in generally good with a low incidence of AE.

*Post marketing experience*

Descriptive analysis of worldwide reported safety data was prepared to additionally support the safety aspect of combined use of losartan + amlodipine in clinical practice.

The presented data included the time interval from 2009 to 2012.

## 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 Good Vigilance Practice module, the Summary is considered acceptable.

### *IV.6.2 Risk Management Plan*

| *Summary of safety concerns* | |
|---|---|
| Important identified risks | • Hypotension.<br>• Hepatic impairment.<br>• Renal impairment and renal failure.<br>• Hypersensitivity reactions.<br>• Hyperkalaemia.<br>• Foetotoxicity and neonatal toxicity.<br>• Rhabdomyolysis and muscle disorders.<br>• Interaction with CYP3A4 inhibitors including grapefruit juice.<br>• Interaction with simvastatin.<br>• Interaction with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels.<br>• Interaction with NSAIDs.<br>• Renal dysfunction, hypotension and hyperkalaemia as consequence of dual RAAS blockade |
| Important potential risks | • Parkinsonism and Parkinson's disease.<br>• Interstitial lung disease.<br>• Teratogenicity.<br>• Interaction with CYP3A4 inducers.<br>• Medication errors including overdose.<br>• Off-label use. |

| *Summary of safety concerns* | |
|---|---|
| Missing information | • Use in paediatric population.<br>• Use in patients who have had kidney transplantation recently.<br>• The use by pregnant women during the first trimester of pregnancy or the use by breast-feeding women.<br>• Long-term use of the combination. |

*Pharmacovigilance Plan*: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to the products of Losartan/Amlodipine 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets. No additional activities are proposed.

*Risk Minimisation Measures*: routine measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to the products of Losartan/Amlodipine 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated 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 marketing authorisation holder shall submit the first periodic safety update report for this product within 3 years following authorization of the marketing authorisation holder's first losartan/amlodipine film-coated tablets with the same composition in the HU/H/0350/001-004/DC procedure (06. 01. 2014). Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## IV.7 Discussion on the clinical aspects

The application concerns fixed combinations of losartan and amlodipine. The indication is substitution therapy for the treatment of essential hypertension, in patients already controlled with the combination of losartan and amlodipine, taken at the same dose level.

To support the application the applicant has adequately demonstrated bioequivalence between the combination and co-administered reference products: monocomponent losartan and amlodipine products.
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 Decentralised Procedure application concerns fixed combinations of losartan (potassium salt) and amlodipine (as besilate): Losartan/Amlodipine Krka 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated 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 the combination of losartan and amlodipine, taken at the same dose level.

The applicant has adequately demonstrated bioequivalence between one strength of the fixed combination and reference products containing the two active principles in monocomponent preparations, marketed in the European Union. This can be extended to the other strengths.

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 found the application approvable and have granted marketing authorisation for Losartan/Amlodipine Krka 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg and 100 mg/10 mg film-coated tablets.

### V.2 Classification

Prescription-only medicine

## 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 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 |
|---|---|---|---|---|---|---|
| | | | | | | |