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

Public Assessment Report

Name of the Product:

Tenloris

50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg, 100 mg/10 mg

(losartan potassium/amlodipine besilate)

Procedure number:
HU/H/0350/001-004/DC

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

Date: 19 June 2014

CONTENT

LAY SUMMARY

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Tenloris (in Poland: Alortia) 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg, 100 mg/10 mg film-coated tablets from Krka, d.d.

The active substances are losartan potassium and amlodipine besilate. Each
- 50 mg/5 mg film-coated tablet contains 50 mg losartan potassium and 6.94 mg amlodipine besilate
- equivalent to 5 mg amlodipine;
- 50 mg/10 mg film-coated tablet contains 50 mg losartan potassium and 13.88 mg amlodipine besilate equivalent to 10 mg amlodipine;
- 100 mg/5 mg film-coated tablet contains 100 mg losartan potassium and 6.94 mg amlodipine besilate equivalent to 5 mg amlodipine;
- 100 mg/10 mg film-coated tablet contains 100 mg losartan potassium and 13.88 mg amlodipine besilate equivalent to 10 mg amlodipine.

The other ingredients (excipients) in the tablet core are: 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).

The other ingredients (excipients) in the film coating of
- 50 mg/5 mg film-coated tablets are iron oxide, red (E172); iron oxide, yellow (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b);
- 50 mg/10 mg film-coated tablets are iron oxide, red (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b);
- 100 mg/5 mg film-coated tablets are iron oxide, red (E172); poly(vinyl alcohol); titanium dioxide (E171); macrogol 3000 and talc (553b);
- 100 mg/10 mg film-coated tablets are 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, slightly biconvex;
- 50 mg/10 mg film-coated tablets are red-brown, oval, slightly biconvex;
- 100 mg/5 mg film-coated tablets are pink, oval, biconvex;
- 100 mg/10 mg film-coated tablets are pale brownish yellow, oval, biconvex.

The film-coated tablets are available in boxes in blisters.

The Tenloris film-coated tablets contain two active substances called losartan and amlodipine. 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.

Tenloris film-coated tablets are 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 Tenloris film-coated tablets

Patients must not take Tenloris film-coated tablets if they

- 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 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 taking Tenloris film-coated tablets in early pregnancy - see Pregnancy).
- have a liver that is function is severely impaired.

Warnings and precautions

Patients must tell their doctor if they think they are (or might become) pregnant. Tenloris film-coated tablets are is not recommended in early pregnancy, and must not be taken by those who are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

It is important that patients consult their doctor before taking Tenloris film-coated tablets if they

- have had a history of angiooedema (swelling of the face, lips, throat, and/or tongue, see also section possible side effects);
- suffer from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in the body;
- receive diuretics (medicines that increase the amount of water that you pass out through the kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in the body;
- are known to have narrowing or blockage of the blood vessels leading to the kidneys or if they have received a kidney transplant recently;
- liver function is impaired;
- suffer from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias. Special caution is necessary when they are treated with a ß-blocker concomitantly;
- have problems with their heart valves or heart muscle;

- suffer 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);
- you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland);
- have had a recent heart attack;
- have or have had a severe increase in blood pressure (hypertensive crisis);
- are elderly and their dose needs to be increased.

Children and adolescents

The use of Tenloris film-coated tablets in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Tenloris film-coated tablets

Patients should consult their doctor if taking, have recently taken or might take any other medicines. Particular care should be taken with the following medicines while under treatment with Tenloris film-coated tablets:
- 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.

Tenloris film-coated tablets may affect or be affected also by other medicines, such as:
- ketoconazole, itraconazole (anti-fungal medicines),
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV),
- rifampicin, erythromycin, clarithromycin (antibiotics),
- 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 Tenloris film-coated tablets without close supervision by a doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Tenloris film-coated tablets with food and drink

Grapefruit juice and grapefruit should not be consumed by people who are taking Tenloris film-coated tablets. 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 Tenloris.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they might become pregnant or are planning to have a baby, ask consult their doctor for advice before taking this medicine.

Pregnancy: The doctor will normally advise stopping taking Tenloris film-coated tablets before the patient becomes pregnant or as soon as they know they are pregnant and will advise them to take another medicine instead of Tenloris for it is not recommended in early pregnancy, and must not be taken when women are more than 3 months pregnant, as it may cause serious harm to the baby if used after the third month of pregnancy.

Breast-feeding: Tenloris film-coated tablets are not recommended for mothers who are breast-feeding, and their doctor may choose another treatment for those who wish to breast-feed, especially if the baby is a new-born, or born prematurely.

Driving and using machines

Tenloris film-coated tablets may affect the ability to drive or use machines. If the tablets make somebody feel sick, dizzy or tired, or cause a headache, do not drive or use machines and contact the doctor immediately.

Tenloris film-coated tablets contain lactose

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

How to take Tenloris film-coated tablets

The recommended dose is one tablet per day.

The tablets should be swallowed with a glass of water, with or without food. Patients should try to take their daily dose at about the same time each day. Do not take Tenloris film-coated tablets with grape-fruit juice.

It is important that patients continue to take Tenloris until the doctor tells otherwise.

The use of Tenloris film-coated tablets in children and adolescents is not recommended.

What to do if you more Tenloris film-coated tablets were taken then prscribed

If accidentally too many tablets were taken, the patient has to contact the doctor immediately. Taking too many tablets may cause the blood pressure to become low or even dangerously low. Patients 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 patients could lose consciousness.

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

If you a daily dose was missed accidentally, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

Stopping taking Tenloris film-coated tablets

The doctor will advise patients how long to take this medicine. The adverse condition may return if stopping using this medicine before advised.

Possible side effects

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

Patients who experience any of the following, severe side effects after taking this medicine must visit their doctor 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.

Amlodipine

The following common (i.e. it 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 patients should contact their doctor:
- headache, dizziness, sleepiness (especially at the beginning of treatment),
- palpitations (awareness of the 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, or

experiencing any side-effects not listed here, patients should inform their doctor or pharmacist.

Uncommon **(**may affect up to 1 in 100 people):
- mood changes, anxiety, depression, sleeplessness,
- trembling, taste abnormalities, fainting, weakness,
- numbness or tingling sensation in the 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.

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.

Losartan

Common:
- dizziness,
- low blood pressure,
- 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:
- somnolence,
- headache,
- sleep disorders,
- feeling of increased heart rate (palpitations),
- severe chest pain (angina pectoris),
- 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,
- shortness of breath (dyspnoea),
- abdominal pain,
- obstipation,
- diarrhoea,
- nausea,
- vomiting,
- hives (urticaria),
- itching (pruritus),
- rash,
- localised swelling (oedema),
- cough.

Rare:
- 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 (i.e. their 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).

How to store Tenloris film-coated tablets

This medicinal product does not require any special storage conditions.

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

Scientific discussion

during the initial procedure

This module reflects the scientific discussion for the approval of Tenloris 50 mg/5 mg, 50 mg/10 mg, 100 mg/5 mg, 100 mg/10 mg film-coated tablets. The procedure was finalised at 6 January 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

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

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Estonia, Latvia, Lithuania, Poland, Romania and the Slovak Republic) concerned fixed combinations of losartan potassium and amlodipine besilate.

Based on the review of the data on quality, safety and efficacy, the Member States have granted marketing authorisation for Tenloris film-coated tablets 50/5 mg, 50/10 mg, 100/5 mg, 100/10 mg losartan potassium/amlodipine besilate from Krka d.d., Novo mesto. (The name of the product has been Alortia in Poland.)

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 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 reference products. Therefore, the submission contained no additional new clinical or non-clinical data, other than supporting literature where necessary.

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 an increase of the efficacy across a wider spectrum of patients.

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

II. QUALITY ASPECTS

II.1 Introduction

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

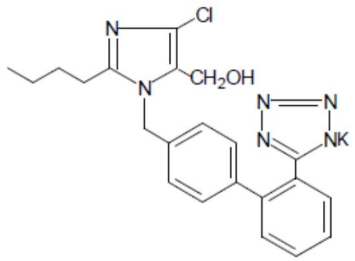
The reference products (for the bioequivalence study) were Lorzaar® Protect 100 mg film-coated tablets (Merck Sharp & Dohme Ltd.) and Istin™ 10 mg tablets (Pfizer) which are monocomponent formulations of losartan potassium and amlodipine besilate, respectively.

II.2 Drug substances

II.2.1 Losartan potassium

For the active substance losartan potassium a certificate of suitability (CEP) has been submitted. Data on the quality and manufacture of the active substance were provided in the submission using the CEP procedure 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 manufacturer consistently produces the same polymorphic form.

The CEP 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, impurity profile of the API containing detailed information about genotoxic impurities, residual solvents and catalysts has been assessed during the CEP procedure.

The active substance is official in the European Pharmacopoeia (Ph. Eur.). Additional specifications has been set for the active substance on the CEP and by the drug product manufacturer, which includes 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 Conference on Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in 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 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 packaging mentioned on the CEP (double polyethylene bag in an aluminium foil bag placed in a fibre drum.)

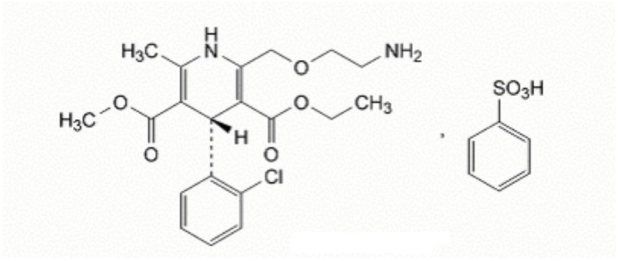
Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

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 active 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 active pharmaceutical ingredient (API) is adequate.

Evidence of the structure, impurity profile of the API 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 has been set for the active substance 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, 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.

Conclusion on stability studies are that all results at controlled room temperature (25°C/60% RH) and at accelerated conditions comply with the proposed specification. No trends are found at long-term and accelerated conditions. Proposed re-test period is acceptable.

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 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* equivalents 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* equivalence 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); iron oxide yellow;
- film-coating: poly(vinyl alcohol) ; titanium dioxide; macrogol 3000; talc, iron oxide red (in 50 mg/5 mg, 50 mg/10 mg and 100 mg/5 mg film-coated tablets); iron oxide yellow (in 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 the *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 Summary of Product Characteristics (SmPC), patient Information 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 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 products.

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 dihydropyridine 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.

No additional 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.

III.5 Ecotoxicology/environmental risk assessment (ERA)

This combination product is indicated for a substitution indication and as such will replace the use of the co-administered single products. Thus, the exposure of the environment to losartan and to amlodipine will not increase by use of this product and an environmental risk assessment will not be required.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of losartan and amlodipine are well-known.

This combination is only for substitution therapy, consequently, there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The product development rationale as outlined by the applicant was primarily related to the benefits of fixed combination therapy in terms of simplification of the therapeutic regimen and increased compliance.

Combining a dihydropyridine calcium channel blocker (CCB, e.g. amlodipine) with and 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 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.

IV.2 Pharmacokinetics

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 the 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 containing losartan potassium and another containing amlodipine besilate.

The composition of the layer of the 100 mg losartan potassium strength is quantitatively proportional to the composition of the 50 mg ones, i.e. the ratio between the amounts of each excipient to the amount of active substance, losartan potassium is the same.

In the layer with 5 mg amlodipine, the amount of filler microcrystalline cellulose, is changed to substitute the amount of active substance, amlodipine besilate, in relation to 10 mg amlodipine layer. The quantity of amlodipine besilate is less than 5% of the amlodipine layer weight;

d) *in vitro* dissolution curves at the required pH values were similar.

The dose-dependent pharmacokinetics in the therapeutic range has also been demonstrated by the Applicant.

Bioequivalence study

The clinical development performed by the Applicant comprised 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 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 to healthy male volunteers under fasting conditions.

The choice of sample size was enough to prove the bioequivalence between the test and reference products with a power of at least 80% and at $\alpha = 5\%$.

The applicant stated that the bioequivalence studies were undertaken according to GCP guidelines.

No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

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 $AUC_{0\text{-}72h}$, C_{max} and T_{max} for amlodipine were determined on the basis of individual concentrations.

The comparison of the test and reference products was performed by the BE Guideline in force during the evaluation.

Confidence intervals were determined for the log-transformed AUC_i, AUC_t, and C_{max} parameters of losartan and $AUC_{0\text{-}72h}$ 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 $AUC_{0\text{-}72h}$ and C_{max} parameters of amlodipine were included within interval 80.00-125.00%.

Summary of the results of the bioequivalence study are shown in the next Tables.

90% Confidence Intervals of ratio of LS-Means (Test/Ref) 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 (Test/Ref) 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, Tenloris (losartan/amlodipine 100 mg/10mg) Krka film-coated tablets formulation, 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) administered simultaneously are bioequivalent under fasting condition.

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

IV.3 Pharmacodynamics

Combining a CCB with an AIIRA has the benefit of reducing blood pressure via different mechanism of action that results in additive blood pressure reductions. This has been also evident in several clinical trials where fixed dose combination losartan + amlodipine were investigated. Furthermore, some of this trial demonstrated significant and rapid blood pressure reductions of the fixed dose combination losartan *plus* amlodipine. AIIRA increase both arterial and venous dilatation, which can counteract CCB-induced 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 rennin 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 angiotensin-II receptor antagonist and a calcium channel blocker provides an effective option for patients with hypertension. Considering the im-

portant role of the renin-angiotensin-aldosterone system (RAAS) 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 of losartan *plus* amlodipine has been investigated in several clinical trials. These trials were mostly randomised, multicentre and double-blind trials and some of them compared the fixed dose combination to either amlodipine monotherapy, losartan monotherapy or to them both.

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 the 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 the fixed dose combination of losartan 50 mg plus amlodipine 5 mg or that of 50 mg/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 plus amlodipine group and 75 amlodipine monotherapy group. A total of 86 treatment emergent adverse events 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 the fixed dose combination and amlodipine 10 mg monotherapy were compared in hypertensive patients who responded 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 adverse events. Overall the fixed dose combination exhibited a safety profile generally comparable to amlodipine 10 mg monotherapy. Furthermore, in the fixed dose combination 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/amlodipine 50mg/5 mg, 100 mg/5 mg, 50mg/10 mg, 100mg/10 mg 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 adverse events were reported as mild to moderate (>95 %) and included dizziness, headache, chest discomfort and reflux esophagitis. There were no reports of serious adverse events 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 adverse events.

Post-marketing experience

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

The applicant presented convincing safety data for amlodipine, losartan and combined use of losartan + amlodipine.

IV.6 Pharmacovigilance

IV.6.1 Pharmacovigilance system

The Applicant has provided the Summary of the Pharmacovigilance (PV) System of KRKA (d.d, Novo mesto, Slovenia, and stated that as Marketing authorisation Holder has the services of a qualified person responsible for pharmacovigilance (QPPV) and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. Member state of the QPPV residence: Slovenia. Location of the Pharmacovigilance System Master File: Slovenia.

IV.6.2 Risk Management Plan

Summary

Safety concern	*Proposed pharmacovigilance activities (routine)*	*Proposed risk minimisation activities (routine)*
Important identified risks		
Hypotension	Routine pharmacovigilance SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR.	SmPC sections 4.3, 4.4, 4.5 and 4.8.
Hepatic impairment	Routine PV. SmPC wording in place.	SmPC sections 4.2, 4.3, 4.4 , 4.8 and 5.2.

	Cumulative and periodical review of all cases reported from any source in the regular PSUR	.
Renal impairment and renal failure	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR	SmPC sections 4.2 ,4.4, 4.5 and 4.8.
Hypersensitivity reactions	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR.	SmPC sections 4.3 , 4.4, and 4.8.
Hyperkalemia	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR.	SmPC sections 4.4, 4.5 and 4.8.
Fetotoxicity and neonatal toxicity	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases.	SmPC sections 4.3 , 4.4, 4.6 and 5.3.
Rhabdomyolysis and muscle disorders	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases	SmPC section: 4.8 Undesirable effects.
Interaction with strong or moderate CYP3A4 inhibitors including grapefruit juice	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases.	SmPC section 4.5.
Interaction with simvastatin	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases	SmPC section 4.5.
Interaction with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases	SPC section: 4.5 Interaction with other medicinal products and other forms of interaction.
Interaction with NSAIDs	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases	SmPC section: 4.5 Interaction with other medicinal products and other forms of interaction. .
Important potentIal risks		
Teratogenicity	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in	SmPC sections 4.3 , 4.4, 4.6 and 5.3

	the regular PSUR. Follow up for all received cases	
Parkinsonism and Parkinson's disease	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases	None proposed
Interstitial lung disease	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases	None proposed
Interaction with CYP3A4 inducers	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR.	SmPC section: 4.5 Interaction with other medicinal products and other forms of interaction.
Medication errors including overdose	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases.	SmPC sections 4.1 and 4.2. .
Off-label use	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received.	SmPC sections 4.1 and 4.2.
Important missing information		
Use in paediatric population	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases up for all received cases.	SmPC sections 4.2 and 4.4. .
Use in patients who have had kidney transplantation recently	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases up for all received cases.	SmPC section 4.4.
The use by pregnant women during the first trimester of pregnancy or the use by breast feeding women	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases.	SmPC sections 4.3, 4.4 and 4.6.
Long-term use of the combination	Routine PV. SmPC wording in place. Cumulative and periodical review of all cases reported from any source in the regular PSUR. Follow up for all received cases.	SmPC sections 5.1

The proposed safety concerns, pharmacovigilance activities and risks minimisation measures

described in the RMP are accepted.

A detailed Summary of the Risk Management Plan for the health care proffesionals can be found attached in a separate document (RMP Summary VI.1).

IV.6.4 Periodic Safety Update Report (PSUR)

The marketing authorisation holder shall submit the first PSUR update report for these products after 3 years following authorisation. Subsequently, the marketing authorisation holder shall submit PSURs in accordance with the requirements set out in the list of the European Union reference dates (EURD list) provided in line with Article 107c(7) of the Directive 2001/83/EC and published on the European medicines web-portal

IV.7 Discussion on the clinical aspects

This 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.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present Decentralised Procedure application concerns fixed combinations of losartan (potassium salt) and amlodipine (as besilate): Tenloris 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.

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

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 HU/H/0350/	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
B.III.1.a) 3 New certificate from a new manufacturer	1-4/1A/001-004	no	18. April 2014	18 May 2014	approval	no