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Public Assessment Report

Name of the Product:

WAMLOX
5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets

(amlodipine/valsartan)

Procedure number: HU/H/0403/001-003/DC

Marketing authorisation holder: Krka d.d.

Date: 7 April 2016

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states: Hungary as reference member state RMS and the concerned member states CMSs Austria, Bulgaria, Croatia, the Czech Republic, Estonia, Germany, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia have granted the marketing authorisation of the Wamlox 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg (in Germany Amlo-Valsacor) film-coated tablets. The holder of the marketing authorisation is Krka d.d., Novo mesto, Slovenia (in Croatia Krka-Farma d.o.o, in Germany HCS bvba).

The active substances are amlodipine (as amlodipine besilate) and valsartan.

The other ingredients are
- in the tablet core: microcrystalline cellulose, magnesium stearate, croscarmellose sodium, povidone, sodium lauryl sulphate, mannitol and colloidal anhydrous silica;
- in the film coating: polyvinyl alcohol –partially hydrolysed, titanium dioxide, macrogol 3000, talc and yellow iron oxide (E172).

Appearance of the film-coated tablets is as follows.
- The 5 mg/80 mg film-coated tablets are brownish yellow, round, slightly biconvex with bevel edges and with possible dark spots.
- The 5 mg/160 mg film-coated tablets are brownish yellow, oval, biconvex, with possible dark spots.
- The 10 mg/160 mg film-coated tablets are pale brownish yellow, oval, biconvex.

The film-coated tablets are packed in OPA/Alu/PVC-Alu foil blisters in box.

Both the two active substances of Wamlox film-coated tablets help to control high blood pressure.

– 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.
– Valsartan belongs to a group of substances called “angiotensin-II receptor antagonists”. Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Wamlox film-coated tablets are used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

What patients need to know before taking Wamlox film-coated tablets

Those who

- are allergic to amlodipine or to any other calcium channel blockers. This may involve itching, reddening of the skin or difficulty in breathing;
- are allergic to valsartan or any of the other ingredients of this medicine. Those who think they may be allergic, discuss their doctor before taking this medicine;
- have severe liver problems or bile problems such as biliary cirrhosis or cholestasis;
- have severe kidney problems or are having dialysis;
- are more than 3 months pregnant, (see Pregnancy section);
- have severe low blood pressure (hypotension);
- have narrowing of the aortic 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;
- have a high level of sugar in the blood and are suffering from type 2 diabetes (also called non-insulin-dependent diabetes mellitus) while taking a blood pressure lowering medicine called aliskiren

must not take Wamlox film-coated tablets.

Warnings and precautions

Patients must consult their doctor before taking Wamlox film-coated tablets

- if they have been sick (vomiting or diarrhoea);
- if they have liver or kidney problems;
- if they have had a kidney transplant or if they had been told that they have a narrowing of the kidney arteries;
- if they have a condition affecting the renal glands called “primary hyperaldosteronism”;
- if they have had heart failure or have experienced a heart attack. The doctor’s instructions for the starting dose must be followed carefully. The doctor may also check the kidney function;
- if their doctor has told you that they have a narrowing of the valves in the heart (called “aortic or mitral stenosis”) or that the thickness of the heart muscle is abnormally increased (called “obstructive hypertrophic cardiomyopathy”);
- if they have experienced swelling, particularly of the face and throat, while taking other medicines (including angiotensin converting enzyme inhibitors). Experiencing these symptoms, taking Amlodipine/valsartan must be stopped and the doctor contacted straight away. Moreover, such patients should never take Amlodipine/valsartan again;
- if they are taking any of the following medicines used to treat high blood pressure:
    - an ACE inhibitor (for example enalapril, lisinopril, ramipril), in particular if they have diabetes-related kidney problems,
    - aliskiren.

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

Children and adolescents

The use of Wamlox film-coated tablets in children and adolescents (aged below 18 years) is not recommended.

Other medicines and Wamlox film-coated tablets

If the patient is taking, have recently taken or might take any other medicines, the doctor must be informed accordingly. The doctor may need to change the dose or take other precautions. In some cases the patient may have to stop taking one of the medicines. This applies especially to the medicines listed below:

- other medicines used to lower blood pressure, called ACE inhibitors or aliskiren;
- diuretics (a type of medicine also called "water tablets" which increases the amount of urine you produce);
- lithium (a medicine used to treat some types of depression);
- potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
- certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). The doctor may also check your kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);
- preparations from St. John's wort;
- nitro-glycerine and other nitrates, or other substances called "vasodilators";
- medicines used for HIV/AIDS (e.g. ritonavir, indinavir, nelfinavir);
- medicines used to treat fungal infections (e.g. ketoconazole, itraconazole);
- medicines used to treat bacterial infections (such as rifampicin, erythromycin, clarithromycin, talithromycin);
- verapamil, diltiazem (heart medicines);
- simvastatin (a medicine used to control high cholesterol levels);
- dantrolene (infusion for severe body temperature abnormalities);
- medicines used to protect against transplant rejection (ciclosporin).

Wamlox film-coated tablets with food and drink

Grapefruit and grapefruit juice should not be consumed by people who are taking Wamlox film-coated tablets. This is because grapefruit and grapefruit juice can lead to an increase the blood levels of the active substance amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect.

Pregnancy and breast-feeding

Those who think they are (or might become) pregnant must consult their doctor. The doctor will normally advise to stop taking Wamlox film-coated tablets before becoming pregnant or as soon as the patient knows she is pregnant and will advise to take another medicine instead of this. Wamlox film-coated tablets are not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to the baby if used after the third month of pregnancy.

Those who are breast-feeding or about to start breast-feeding must inform their doctor. Wamlox film-coated tablets are not recommended for mothers who are breast-feeding, and the doctor may choose another treatment for those who wish to breast-feed, especially if the baby is new-born, or was born prematurely.

Driving and using machines

This medicine may make feel dizzy. This can affect how well the patient can concentrate. Thus, if the patient is not sure how this medicine will him/her, it is better not to drive, use machinery, or do other activities that concentration is needed on.

How to take Wamlox film-coated tablets

The usual dose of Wamlox film-coated tablets is one tablet per day.

- It is preferable to take the medicine at the same time each day.
- The tablet should be swallowed with a glass of water.
- The Wamlox film-coated tablets can be taken with or without food but not with grape-fruit or grapefruit juice.

Depending on how the patient responds to the treatment, the doctor may suggest a higher or lower dose. The prescribed dose should not be exceeded.

Wamlox film-coated tablets and elderly people (age 65 years or over)

The doctor will exercise caution when increasing the dose.

What to do if more Wamlox film-coated tablets were taken than it should be?
If too many tablets of Wamlox film-coated tablets were taken, or if someone else has taken the patient's tablets, the doctor must be consulted immediately.

What to do if taking of Wamlox film-coated tablets was forgotten?

If taking this medicine was forgotten, the patient should take it as soon as remembering it, then the next dose should be taken at its usual time. However, if it is almost time for the next dose, skip the dose have been missed. Do not take a double dose to make up for a forgotten tablet.

May taking of Wamlox film-coated tablets be stopped by patients?

Stopping the treatment with this medicine may cause the disease to get worse. Taking this medicine should not be stopped unless instructed so by the doctor.

Possible side effects

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

Some side effects can be serious and need immediate medical attention:

A few patients have experienced these serious side effects (may affect up to 1 in 1,000 people). If any of the following happens, the doctor must be informed straight away: allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

Other possible side effects of Wamlox film-coated tablets

Common (may affect up to 1 in 10 people): influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.

Uncommon (may affect up to 1 in 100 people): dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.

Rare (may affect up to 1 in 1,000 people): feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.

Side effects reported with amlodipine or valsartan alone and either not observed with Amlodipine/valsartan combinations or observed with a higher frequency than with Wamlox film-coated tablets:

Amlodipine

Patients who experience any of the following very rare, severe side effects after taking this medicine must consult 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 in breathing;
- severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of the 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 of being very unwell.

The following side effects have been reported. If any of these cause problems or if they last for more than one week, the patient should contact the doctor.

Common (may affect up to 1 in 10 people): dizziness, sleepiness; palpitations (awareness of your heart beat); flushing, ankle swelling (oedema); abdominal pain, feeling sick (nausea).

Uncommon (may affect up to 1 in 100 people): mood changes, anxiety, depression, sleeplessness, trembling, taste abnormalities, fainting, loss of pain sensation; visual disturbances, visual impairment, ringing in the ears; low blood pressure; sneezing/runny nose caused by inflammation of the lining of the nose (rhinitis); indigestion, vomiting (being sick); hair loss, increased sweating, itchy skin, skin discolouration; 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, pain, feeling unwell, muscle pain, muscle cramps; 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 number 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); 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.

Valsartan

Not known (frequency cannot be estimated from the available data): Decrease in red blood cells, fever, sore throat or mouth sores due to infections; spontaneous bleeding or

bruising; high level of potassium in the blood; abnormal liver test results; decreased renal functions and severely decreased renal functions; swelling mainly of the face and the throat; muscle pain; rash, purplish-red spots; fever; itching; allergic reaction.

How to store Wamlox film-coated tablets

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

Store it below 30 °C.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Wamlox 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets. The procedure was finalised at 16 December 2015. 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*, applications have been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure applications with reference member state, RMS: Hungary, concerned member states, CMS: Austria, Bulgaria, Croatia, the Czech Republic, Estonia, Germany, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia concerned the generic versions of fixed combinations of amlodipine/valsartan 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets: Wamlox (in Germany Amlo-Valsacor) film-coated tablets.

The applications were submitted pursuant to Article 10(1) of the above Directive (so called "generic application"), therefore contained no new clinical or preclinical data, other than supporting literature where necessary, in accordance with the provisions of the Article.

The reference product was the originator, Exforge 5mg/80 mg, 5mg/160 mg, 10 mg/160 mg film-coated tablets by Novartis Europharm Ltd., authorised for marketing since January 17th 2007.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Wamlox 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, film[M1]-coated tablets from Krka d.d., Novo mesto, Slovenia (in Croatia: Krka-Farma d.o.o., in Germany: HCS bvba).

The products are indicated for the following conditions: treatment of essential hypertension. Wamlox film-coated tablets are indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

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

II. QUALITY ASPECTS

II.1 Introduction

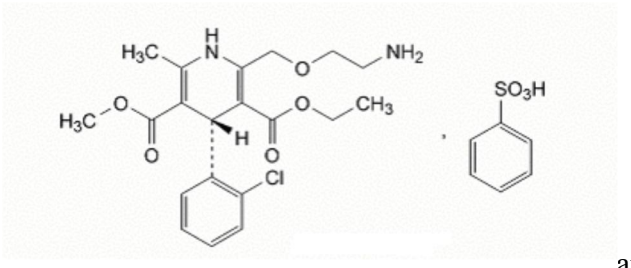
The chemical-pharmaceutical assessment report concerns the application of Wamlox 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Krka d.d., Novo mesto. The reference products are Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets (containing 5, 10 mg amlodipine and 80 mg, 160 mg valsartan as active ingredients) which were the original products of Novartis.

II.2 Drug substances

II.2.1 Amlodipine besilate

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

INN 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. The polymorphism is discussed satisfactorily.

The substance is specified according to the requirements of the current Ph. Eur. monograph with additional requirements for residual solvents, particle size distribution and microbial impurities.

The Ph. Eur. specification includes the following tests for amlodipine besilate: appearance, solubility, identification (IR), optical rotation, water content, sulphated ash, related substances (HPLC) and assay.

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

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

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

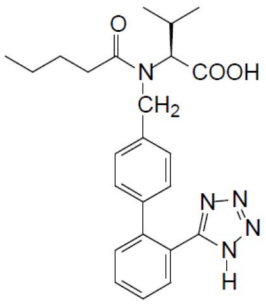
A retest period and the packaging material (double polyethylene bags (outer black) placed inside a fibre board drum) have been mentioned on the CEP.

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

II.2.2 Valsartan

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

INN name: valsartan
Chemical name: (2S)-3-Methyl-2-[pentanoyl[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]amino] butanoic acid
Structure:



The active substance is white to almost white hygroscopic powder, freely soluble in anhydrous ethanol, sparingly soluble in dichloromethane, practically insoluble in water. The substance shows polymorphism and stereoisomerism. The manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph. Eur. monograph with additional requirements for residual solvents, impurities and particle size distribution.

The Ph. Eur. specification includes the following tests for appearance, solubility, identification (by IR), specific optical rotation, enantiomeric purity (HPLC), chromatographic purity (HPLC), heavy metals, water content, sulphated ash and assay (potentiometry).

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

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

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

A retest period and the packaging material (a polyethylene bag placed in an aluminium triplex bag) 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 film-coated tablets containing amlodipine besilate and valsartan as drug substances in 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets, the branded original products of Novartis.

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

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

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies products with the following appearances, compositions and packaging were obtained.

5mg/80 mg	Brownish yellow, round, slightly biconvex, film-coated tablets with bevel edges and with possible dark spots.

5 mg/160 mg	Brownish yellow, oval, biconvex, film-coated tablets with possible dark spots.
10 mg/160 mg	Pale brownish yellow, oval, biconvex, film-coated tablets.

The excipients used in the finished products are microcrystalline cellulose, mannitol, magnesium stearate, croscarmellose sodium, povidone K25, silica colloidal anhydrous, sodium lauryl sulphate, yellow iron oxide, and[M2] Opadry II white (macrogol 3000, titanium dioxide, talc and partially hydrolyzed poly(vinyl alcohol)). All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method 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 products specifications are satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the products is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with the storage restriction **"***Do not store above 30°C*" is approved.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Introduction

No specific non-clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of the Directive 2001/83/EC as amended.

The non-clinical part of the application consisted of literature reviews. The overview has been written by a qualified person and is satisfactory.

III.2 Pharmacology

The *amlodipine* component of amlodipine/valsartan inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals.

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT_2, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.

III.3 Pharmacokinetics

Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine

Amlodipine bioavailability is unaffected by food ingestion.

Distribution: in vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation: amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination: amlodipine elimination from plasma is biphasic.

Valsartan

Absorption: food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although a few hours post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation: valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination: valsartan shows multiexponential decay kinetics ($t_{½}\alpha$ <1 h and $t_{½}\beta$ about 9 h). Valsartan is primarily eliminated in faeces and urine, mainly as unchanged drug.

III.4 Toxicology

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times, based on patient weight of 50 kg the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Rats and mice treated with amlodipine in the diet for two years, at concentrations

calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

Valsartan

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring. These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine.

Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Amlodipine/valsartan

Adverse reactions observed in animal studies with possible clinical relevance were as follows.

Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen

in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Amlodipine/valzartán Krka Pharma film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamic, pharmacokinetic and toxicological properties of both amlodipine and valsartan are well known. Since both compounds are widely used, well-known active substance, no further studies are required and the applicant provides none. Therefore, overview based on literature review is appropriate.

From non-clinical aspects the products are approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns the fixed combinations of amlodipine/valsartan 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets under trade name Wamlox and refers to Article 10(1) "generic application". To support the application, the applicant has submitted the report of a single dose bioequivalence study with the amlodipine/valsartan 10 mg/160 mg film-coated tablets under fasting conditions. Biowaiver has been requested for the other strengths. New clinical data other than a bioequivalence study report have not been supplied with this application and none is required for an application of this type. A clinical overview has been written by a qualified person and is satisfactory.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Amlodipine

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Volume of distribution is approximately 21 l/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Valsartan shows multiexponential decay kinetics ($t_{½}\alpha$ <1 h and $t_{½}\beta$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Amlodipine/valsartan combination

Both amlodipine and valsartan exhibit linear pharmacokinetics. Pharmacokinetic interaction is unlikely as they have no competition in any of the pharmacokinetic processes neither they have enzyme inducing properties. Although amlodipine is metabolized by CYP3A4 it has no effect on valsartan that is metabolized in a low percentage only.

IV.2.2 Bioequivalence study

The applicant has submitted the full reports of the following bioequivalence study: comparative, Randomised, Single-Dose, 2-Way Crossover Bioavailability Study of Two 10 mg/160 mg Amlodipine Besilate + Valsartan Formulations In Healthy Adult Volunteers Under Fasting Conditions.

Determination of valsartan and amlodipine in plasma samples was performed using a validated LC/MS/MS method.

Pharmacokinetic variables: C_{max}, AUCt, AUCi, residual area (RAUC), T_{max}, T_{half} and Kel for valsartan while C_{max}, AUC_{0-72}, and T_{max} for amlodipine were determined from individual plasma concentration – time profiles using model-independent approach.

An analysis of variance (ANOVA) followed by the calculation of the classic (shortest) 90% confidence intervals for the test to reference intraindividual LS-Means ratios of AUC_i, AUC_t and C_{max} parameters for valsartan was performed. The data were ln-transformed prior to analysis.

An analysis of variance (ANOVA) followed by the calculation of the classic (shortest) 90% confidence intervals for the test to reference intraindividual LS-Means ratios of AUC_{0-72} and C_{max} parameters for amlodipine was performed. The data were ln-transformed prior to analysis.

Bioequivalence was concluded if the 90% confidence intervals for the ratio (test/ reference) of the LS-Means of AUC_{0-72} and C_{max} parameters for amlodipine and AUC_t and C_{max} for valsartan were included within interval 80.00-125.00%.

Descriptive statistics were also done for all pharmacokinetic parameters.

Bioequivalence evaluation of valsartan

Pharmacokinetic parameter	*Geometric Mean Ratio Test/Ref*	*Confidence Intervals*	*CV%*[1]
AUC_t	93.58%	83.82% – 104.47%	38.6 %
C_{max}	91.22%	80.98% – 102.74%	42.0 %

[1]Estimated from the Residual Mean Squares.

Bioequivalence evaluation of amlodipine

Pharmacokinetic parameter	*Geometric Mean Ratio Test/Ref*	*Confidence Intervals*	*CV%*[1]
$AUC_{(0-72)}$	98.93%	96.20% – 101.74%	9.5 %
C_{max}	99.68%	96.36% –103.11%	11.5 %

[1]Estimated from the Residual Mean Squares

Formulation, period and sequence effects for un-transformed and ln-transformed data were found to be statistically insignificant.

Overall conclusion on the study results:

The data provided have proven the bioequivalence of Wamlox 10 mg/160 mg film-coated tablet with the originator Exforge® 10 mg/160 mg film-coated tablet.

Biowaiver for the other strengths:

The other strengths have fulfilled all the criteria for the biowaiver laid in the Guideline on the *Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1). The biowaiver for the other strengths can be granted.

IV.3 Pharmacodynamics

Amlodipine belongs to the dihydropiridine Ca^{++}-channel blockers. It inhibits the calcium influx through the L-type (slow) Ca^{++}-channels. As calcium is an essential mediator of smooth muscle contraction amlodipine relaxes smooth muscles especially the blood vessels. By this vasodilating effect amlodipine reduces the peripheral vascular resistance this way it reduces blood pressure and the afterload for the heart as well. By decreasing afterload it reduces the oxygen de-

mand of the heart. Furthermore, dilation of coronary arteries improves the cardiac oxygen supply. These two latter mechanisms may result in preventing angina attacks in chronic stable angina as well as in Prinzmetal's angina (coronary spasm). Despite its marked vasodilatory effect it does not cause strong reflex tachycardia. The negative inotropic effect of amlodipine on the heart is weak provided by its good vasoselectivity over the cardiac L-type channels.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of its administration.

In patients with angina, by once daily administration it increases total exercise time, time to angina onset, and time to significant ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood glucose and serum uric acid and it was suitable for use in patients with asthma. It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood glucose and serum uric acid and it was suitable for use in patients with asthma

Valsartan is a nonpeptide, orally active, and specific of angiotensin II (AII) antagonist or angiotensin receptor blocker (ARB). It selectively, competitive and insurmountable inhibits the actions of AII at the AII type 1 (AT1) receptor subtype which is responsible for most of the known effects of AII. It blocks the vasoconstrictor and aldosterone-secreting effects of AII by selectively blocking the binding of AII to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for AII synthesis. Blockade of the AII receptor inhibits the negative regulatory feedback of AII on renin secretion, but the resulting increased plasma renin activity (PRA) and AII circulating levels do not overcome the effect of valsartan on blood pressure. Because valsartan does not inhibit ACE (kininase II) it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Even in high concentrations, valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation

Amlodipine/valsartan combination: the justification for a combination of amlodipine and valsartan is based on their synergistic effects in their antihypertensive mechanism. Both amlodipine and valsartan are two of the most commonly prescribed antihypertensive drugs in their classes. Their efficacy in lowering systolic and diastolic blood pressure and reducing cardiovascular events has been demonstrated in several randomized trials.

There is ample evidence today that dihydropyridine Ca^{++}-channel blockers and ARBs have a positive impact on the cardiovascular, cerebrovascular and renal outcomes of hypertensive patients. This is especially true in high risk patients with multiple cardiovascular risk factors, subclinical target organ damage, or established cardiovascular or renal disease. Amlodipine and valsartan were part of the drug regimens under study in several large hypertension morbidity–mortality trials, and much of the present knowledge on the beneficial effects of Ca^{++}-channel blockers and ARBs in various clinical conditions associated with high blood pressure has been

accumulated using these two compounds. Both amlodipine and valsartan have beneficial effects on cardiovascular morbidity and mortality, as well as protective effects on renal function.

IV.4 Clinical efficacy

The efficacy of the amlodipine/valsartan combination has already been demonstrated during the clinical development program of the innovator product.

IV.5 Clinical safety

The clinical safety of both amlodipine and valsartan as well as the amlodipine/valsartan combination has been well established.

No special adverse reactions occurred during the bioequivalence study.

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 Hyperkalemia Hypersensitivity reaction including angiodema Pulmonary oedema – in patients with pre-existing heart failure NYHA grades III and IV Cardiovascular events and death – in patients with congestive heart failure Decreased renal function– especially in patients with renal artery stenosis, pre-existing renal impairment, heart failure, post-myocardial infarction, dual blockade of RAAS Drug interactions – NSAIDs, lithium, aliskiren and other antihypertensives, dantrolene, drugs affecting CYP3A4, grapefruit juice, simvastatin, potassium-sparing diuretics, potassium supplements,

	salt substitutes containing potassium and other substances that may increase potassium levels, inhibitors of uptake transporters Fetotoxicity (with use in 2nd or 3rd trimester of pregnancy)
Important potential risks	Teratogenicity (with use during 1st trimester of pregnancy) Reproductive toxicity Medication error
Missing information	Use during breast feeding Safety in patients with recent kidney transplantation Safety and efficacy in hypertensive crisis

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Wamlox 5 mg/80 mg, 5mg /160 mg and 10 mg/160 mg mg film-coated tablets. No additional activities are proposed.

Risk minimisation measures: routine risk minimisation measures (i.e. wording in SmPC, patient information and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Wamlox 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 requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

The present application contains an adequate review of published clinical data and the bioequivalence between Wamlox 10 mg/160 mg film-coated tablets and Exforge® 10 mg/160 mg film-coated tablets has been shown. The biowaiver for the other strengths can also be granted.

The SmPC and package leaflet are in line with that of the originator product Exforge® and comply with the recent QRD template (version 9) therefore they are acceptable.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Wamlox 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets, generic versions of these fixed combinations. The applicant and the future holder of authorisation is Krka d.d. in the RMS.

The products are indicated for the following conditions: treatment of essential hypertension. Wamlox film-coated tablets are indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Exforge 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets by Novartis Europharm Ltd., authorised for marketing since 2007.

To support the application the applicant has adequately proven the bioequivalence of Wamlox 10 mg/160 mg film-coated tablet with the originator Exforge® 10 mg/160 mg film-coated tablets.

The other strengths have fulfilled all the criteria for the biowaiver laid in the Guideline on the *Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1). The biowaiver for the other strengths can be granted.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Wamlox 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg 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