IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amlodipine/Valsartan Krka 5 mg/ 160 mg film-coated tablets
Amlodipine
Valsartan
PA1347/055/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number HU/H/0404/001-005/DC with Hungry as RMS. The responsibility of RMS was transferred to Ireland on 26/04/2022 under procedure number IE/H/1150/001-005/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1347/055/001-005
Marketing Authorisation Holder: KRKA, d.d., Novo mesto

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The Hungarian public assessment report published at the time of the initial marketing authorisation is provided herein

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, con- cerned member states, CMS: Belgium, Finland, Greece, France, Ireland, Norway (except the 5 mg/320 mg and 10 mg/320 mg strengths), Portugal and Spain concerned the generic ver- sions of fixed combinations of amlodipine/valsartan

5 mg/80 mg (HU/H/0404/001)
5 mg/160 mg (HU/H/0404/002)
10 mg/160 mg (HU/H/0404/003)
5 mg/320 mg (HU/H/0404/004)
10 mg/320 mg (HU/H/0404/005)

film-coated tablets (Amlodipine/valsartan Krka, in Greece Amlodipine/valsartan/TAD film- coated tablets).

The applications were submitted according to Article 10 of the above Directive (so called "generic i.e. hybrid 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/160mg, 10mg/160mg 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 Amlodipine/valsartan Krka 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 mg film-coated tablets from Krka d.d., Slovenia.

The products are indicated for the following conditions: treatment of essential hypertension. Amlodipine/valsartan Krka 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 Amlodi- pine/valsartan Krka 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 mg film-coated tablets via a decentralized procedure according to Article 10 of Directive 2001/83/EC (i.e. a generic i.e. hybrid 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.

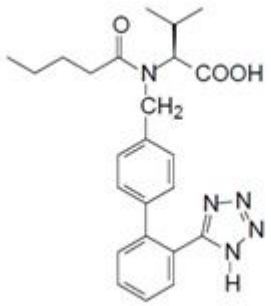
II.2Drug substances

II.2.1 Amlodipine besilate

Data on the quality and manufacture of the active substance were provided in the ap- plicant's submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suit- ability (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 ade- quately 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.

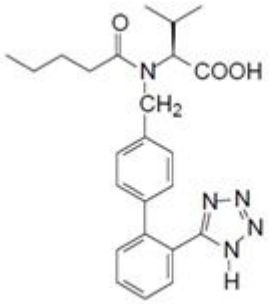
A retest period and the packaging material (double polyethylene bags (outer black) placed inside a fibre board drum) have been mentioned on the CEP.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demon- strated 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. mono- graph with additional requirements for residual solvents, impurities and particle size distribution.

The Ph. Eur. specification includes the following tests for appearance, solubility, iden- tification (by IR), specific optical rotation, enantiomeric purity (HPLC), chromato- graphic 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 manu- facturer 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 meth- ods 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 demon- strated 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, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 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
5 mg/320 mg	Brown, biconvex, capsule shaped film-coated tablets.
10 mg/320 mg	Brownish yellow, biconvex, capsule shaped film-coated tablets with possible dark spots.

The excipients used in the finished products are microcrystalline cellulose, mannitol, magne- sium stearate, croscarmellose sodium, povidone K25, silica colloidal anhydrous, sodium lauryl sulphate, yellow iron oxide, red iron oxide and 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 inprocess 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 com- plied 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 **"***Donotstore above30°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 ac- cordance 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 AT1, which is responsible for the known actions of angiotensin II. The in- creased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT2, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000- fold) greater affinity for the AT1 receptor than for the AT2 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 sub- stance 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 circulat- ing 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 (Cmax) 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 valsar- tan 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 re covered 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/m2 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/valsartan 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 Discussionon 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns the fixed combinations of amlodipine/valsartan 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 mg film-coated tablets under trade name Amlodipine/valsartan KRKA and refers to Article 10 "generic i.e. hybrid 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 re- quired 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 concen- trations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been cal- culated as between 64% and 80%. Amlodipine bioavailability is unaffected by food in- gestion.

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 valsar- tan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases ex- posure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 h post dosing plasma valsartan concentra- tions 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 (t½α <1 h and t½ß about 9 h). Valsar- tan 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/valsartancombination

Both amlodipine and valsartan exhibit linear pharmacokinetics. Pharmacokinetic inter- action 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), Tmax, Thalf and Kel for valsartan while Cmax, AUC0-72, and Tmax for amlodipine were determined from individ- ual 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 AUCi, AUCt and Cmax 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

AUC0-72 and Cmax 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 AUC0-72 and Cmax parameters for amlodipine and AUCt and Cmax 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 RatioTest/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 RatioTest/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 Amlodipine/valsartan KRKA 10 mg/160 mg film-coated tablet with the originator Exforge® 10 mg/160 mg film-coated tablet.

Biowaiver for the others trengths:

The other strengths have fulfilled all the criteria for the biowaiver laid in the Guideline on the *InvestigationofBioequivalence* (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 in- flux 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 vascodilating 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 demand 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 pa- tients with asthma

*Valsartan*is a nonpeptide, orally active, and specific of angiotensin II (AII) antagonist or an- giotensin 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 am- lodipine 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 bene- ficial effects on cardiovascular morbidity and mortality, as well as protective effects on renal function.

IV.4 Clinicalefficacy

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

IV.5 Clinicalsafety

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 Sum- mary is considered acceptable.

IV.6.2Risk Management Plan

Summary of safety concerns	
Important identified risks	Hypotension Hyperkalemia Hypersensitivity reaction including angiodema Pulmonary oedema – in patients with pre-existing heart failure NY HA 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 antihyper- tensives, dantrolene, drugs affecting CYP3A4, grapefruit juice, simvastatin, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may in- crease 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 Krka's product of Amlodi- pine/Valsartan 5 mg/80 mg, 5mg /160 mg, 10 mg/160 mg, 5 mg/320 mg, 10 mg/320 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 con- sidered sufficient to manage all of the safety concerns connected to Krka's product of Amlodipine/Valsartan 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 Discussionon 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 bioe- quivalence between Amlodipine/valsartan Krka 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 CONCLUSIONS

V.1 Summary

The present applications concern Amlodipine/valsartan Krka 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 mg film-coated tablets, generic versions of these fixed combinations. The applicant and the future holder of authorisation is Krka d.d.

The products are indicated for the following conditions: treatment of essential hypertension. Amlodipine/valsartan Krka 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 of Directive 2001/83/EC (generic i.e. hybrid 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 Amlodi- pine/valsartan KRKA 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 quali- ty 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 Amlodipine/valsartan Krka 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg and 10 mg/320 mg film-coated tablets.

VI. REVISION DATE

April 2024

VII. UPDATES

SCOPE	**PROCEDURE NUMBER**	**PRODUCT INFORMATION AFFECTED**	**DATE OF START OF PROCEDURE**	**DATE OF END OF PROCEDURE**
RMS transfer	From HU/H/0404/001-005 to IE/H/1150/001-005/DC	N/A	26/04/2022	N/A