

Public Assessment Report

Name of the Product:

Valonor

5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg filmtabletta
(amlodipine/valsartan)

Procedure number: HU/H/0400/001-003/DC

Marketing authorisation holder: Elpen Pharmaceutical Co. Inc.

Date: 12 April 2016

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE
ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states: Hungary as reference member state RMS and Cyprus, France, Germany, Greece and Spain as concerned member states CMSs have granted marketing authorisations to Valonor 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, film-coated tablets.

The holder of the marketing authorisation is Elpen Pharmaceutical Co. Inc.

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

The other ingredients are cellulose microcrystalline, crospovidone, silica colloidal anhydrous, magnesium stearate, hypromellose, iron oxide yellow (E172), titanium dioxide, macrogol and talc. The tablets 10 mg/160 mg contain also iron oxide red (E172).

Appearance of the film-coated tablets is as follows.

- The 5 mg/80 mg film-coated tablets are dark yellow to brownish and round.
- The 5 mg/160 mg film-coated tablets are dark yellow to brownish and oblong.
- The 10 mg/160 mg film-coated tablets are light yellow and oblong.

The film-coated tablets are packed in PVC/PVDC– Alu blisters or in PVC/PVDC– Alu perforated unit dose blisters.

Both the two active substances of Valonor 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.

Valonor 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 Valonor 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 diabetes or impaired kidney function and are treated with a blood pressure lowering medicine containing aliskiren

must not take Valonor film-coated tablets.

Warnings and precautions

Patients must consult their doctor before taking Valonor 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 Valonor must be stopped and the doctor contacted straight away. Moreover, such patients should never take Valonor 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 Valonor film-coated tablets in children and adolescents (aged below 18 years) is not recommended.

Other medicines and Valonor 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:

- ACE inhibitors or aliskiren;
- diuretics (a type of medicine also called “water tablets” which increases the amount of urine production);
- 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 the kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);
- preparations from St. John’s wort;
- nitroglycerine 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, telithromycin);
- 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).

Valonor film-coated tablets with food and drink

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

The usual dose of Valonor 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 Valonor film-coated tablets can be taken with or without food but not with grapefruit 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.

Valonor 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 Valonor film-coated tablets were taken than it should be?

If too many tablets of Valonor 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 Valonor 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 Valonor 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, Valonor 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 patients). 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 Valonor film-coated tablets

Common (may affect up to 1 in 10 patient): 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 patient): 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 patient): 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 Valonor or observed with a higher frequency than with Valonor 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 patient): 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 patient): 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, 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, blistering skin (sign of condition called dermatitis bullous).

How to store Valonor 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 Valonor 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets. The procedure was finalised at 23 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: Cyprus, France, Germany, Greece and Spain 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: Valonor film-coated tablets.

Amlodipine/valsartan combinations contain two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new non-clinical and clinical data, other than supporting literature where necessary and the bioequivalence study. The reference medicinal products for these applications were Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets (Novartis Europharm Ltd.), authorised for marketing since January 2007. The applicant has adequately demonstrated bioequivalence between its products and reference products.

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Valonor 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets from Elpen Pharmaceutical Co. Inc.

The product is indicated for treatment of essential hypertension 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 Valonor 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 Elpen Pharmaceutical Co. Inc. 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, respectively) which were the original products of Novartis.

II.2 Drug substances

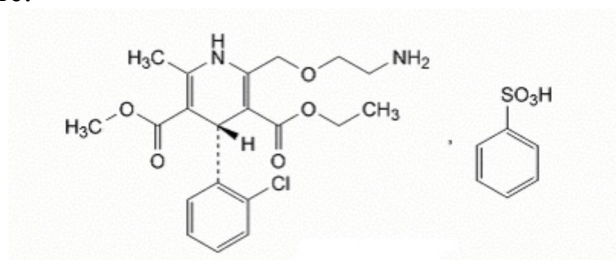
II.2.1 Amlodipine besilate

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 manufacturer consistently produces the same polymorphic form.

The substance is specified according to the requirements of the current Ph. Eur. monograph with additional requirements for a residual solvent.

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 PE drum) have been mentioned on the CEP.

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

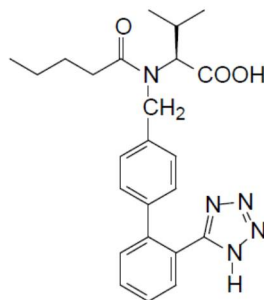
II.2.2 Valsartan

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'-(1H-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.

The Ph. Eur. specification includes the following tests for appearance, solubility, identification, 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 (double PE bags inside a triple laminated aluminium bag) have been mentioned on the CEP.

GMP compliance of the drug substance 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 pharmaceuticals has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

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

- 5 mg/80 mg: dark yellow to brownish, round (diameter: 8 mm), film-coated tablets;
- 5 mg/160 mg: dark yellow to brownish, oblong (14.2×5.7 mm) film-coated tablets;
- 10 mg/160 mg: light yellow, oblong (14.2×5.7 mm) film-coated tablets.

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

The excipients used in the finished products are microcrystalline cellulose, crospovidone, silica colloidal anhydrous, magnesium stearate and film-coating containing hypromellose, yellow iron oxide, macrogol 3350, titanium dioxide, talc or hypromellose, yellow iron oxide, red iron oxide, macrogol 3350, titanium dioxide, talc. All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished 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.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 21 months with the storage restriction “*Store below 25°C*” is approved.

The SmPC, patient information (package) leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to 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

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 AT₁, which is responsible for the known actions of angiotensin II. The increased 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 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 ($t_{1/2\alpha} < 1$ h and $t_{1/2\beta}$ 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

Since Valonor 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 points of view the products are approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns Valonor, 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 and refers to Article 10(1) of the Directive 2001/83/EC, i.e. “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, accompa-

nied 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 ($t_{1/2\alpha} < 1$ h and $t_{1/2\beta}$ 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

In support of these applications, the applicant submitted the following bioequivalence study: a single dose, randomized, two-period, two-treatment, two-sequence, crossover bioavailability study with the on applicant's test product Valonor 10/160 mg film-coated tablets (Elpen Pharmaceutical Co. Inc.) versus Exforge 10 mg/160 mg film-coated tablets (Novartis Europharm Limited) in healthy volunteers under fasting conditions.

In each study period each subject received either one single dose (one tablet) of test or reference study medications according to the randomization schedule under fasting condition.

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

The pharmacokinetic results are presented in Tables below.

It can be seen that the results derived from the analysis of log-transformed primary pharmacokinetic parameters (C_{\max} , $AUC_{(0-t)}$ of valsartan and $AUC_{(0-72)}$ of amlodipine), namely the test/reference T/R ratios of group LS means and their 90% confidence intervals were included within the predefined acceptance interval of 80% - 125%.

Bioequivalence evaluation of amlodipine:

<i>Pharmacokinetic parameter</i>	<i>Ratio T/R</i>	<i>Confidence interval</i>	<i>CV%</i>
AUC ₍₀₋₇₂₎	1.0277	1.0009 – 1.0572	7.9 %
C _{max}	0.9746	0.9408 – 1.0147	10.9 %

AUC₍₀₋₇₂₎: area under the plasma concentration-time curve from time zero to 72 hours

C_{max}: maximum plasma concentration

Bioequivalence evaluation of valsartan:

<i>Pharmacokinetic parameter</i>	<i>Ratio T/R</i>	<i>Confidence interval</i>	<i>CV%</i>
AUC _(0-t)	0.9877	0.9345 – 1.1433	29.7 %
C _{max}	0.9663	0.8907 – 1.1683	40.7 %

AUC_{0-t}: area under the plasma concentration-time curve from administration to last observed concentration at time t.

C_{max}: maximum plasma concentration

Thus, the results support the bioequivalence between the applicant's test product and reference product Exforge 10 mg/160 mg film-coated tablets.

Both the study medications were found to be safe and well tolerated.

Biowaiver for the lower strengths

As the lower 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 results and conclusions of the bioequivalence study can be extrapolated to the lower strengths (5mg/80mg and 5mg/160mg).

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none are required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required for applications of this type.

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

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

Risk Minimisation Measures: routine risk minimisation measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Elpen's product of Valonor 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The 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 applications the bioequivalence studies described in section IV.2 are pivotal.

This application contains an adequate review of published clinical data and the bioequivalence between Valonor 10 mg/160 mg film-coated tablets and Exforge® 10 mg/160 mg film-coated tablets has been shown. As the lower strengths meet the biowaiver criteria specified in the Guideline on the *Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1), the results and conclusions of the bioequivalence study can be extrapolated to the 5 mg/80 mg and 5 mg/160 mg strengths.

Approval is recommended from the clinical point of view.

National Institute of Pharmacy
and Nutrition
Budapest, Hungary

Valonor 5 mg/80 mg,
5 mg/160 mg, 10 mg/160 mg film-coated tablets
HU/H/0400/001-003/DC
Public Assessment Report

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Valonor 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 Elpen Pharmaceutical Co. Inc.

The products are indicated for the following conditions: treatment of essential hypertension 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 and 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 Valonor 10 mg/160 mg film-coated tablets 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 Valonor 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached