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Public Assessment Report

Name of the Product:

NortivanCombi

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

(amlodopine besilate/valsartan)

Procedure number: HU/H/0473/001-003/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 2 June 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the NortivanCombi 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substances are amlodipine (as amlodipine besilate) and valsartan. Each film-coated tablet contains 5 mg or 10 mg amlodipine (as amlodipine besilate) and 80 mg or 160 mg valsartan.

The other ingredients are microcrystalline cellulose, pregelatinised maize starch, crospovidone (type A), sodium starch glycolate (type A), anhydrous calcium hydrogen phosphate, anhydrous colloidal silica, magnesium stearate, lactose monohydrate, hypromellose 15 cP, titanium dioxide (E171), iron oxide yellow (E172) and macrogol 4000.

The appearance of NortivanCombi film-coated tablets (further on: NortivanCombi) is as follows.

- The 5 mg/80 mg strength: round, dark yellow, biconvex film-coated tablets with bevelled edges, diameter is ~ 9 mm, with debossing 5 and 80 divided with score line. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- The 5 mg/160 mg strength: oval, dark yellow, biconvex film-coated tablets with bevelled edges, dimensions are ~14.5 mm x 7.5 mm, with debossing 5 and 160 divided with score line. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- The 10 mg/160 mg strength: oval, yellow, biconvex film-coated tablets with bevelled edges, dimensions are ~14.5 mm x 7.5 mm, with debossing 10 and 160 divided with score line. The film-coated tablet can be divided into equal doses.

NortivanCombi is available in PVC/ACLAR/PVC//Al blisters or in PVC/ACLAR/PVC//Al unit-dose blisters.

NortivanCombi contains two active substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.

- Amlodipine belongs to a group of substances called “calcium channel blockers”. It 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 active substances help to stop the blood vessels tightening. As a result, the blood vessels relax, and blood pressure is lowered.

NortivanCombi is 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 NortivanCombi

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, talk to their doctor before taking NortivanCombi,
- have severe liver problems or bile problems such as biliary cirrhosis or cholestasis,
- are more than 3 months pregnant. (It is also better to avoid NortivanCombi in early pregnancy (see section "Pregnancy and breast-feeding" section),
- have severe low blood pressure (hypotension),
- have narrowing of the aortic valve (aortic stenosis) or cardiogenic shock (a condition where your 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 NortivanCombi. If any of the above applies, the patient must consult the doctor.

Warnings and precautions

Patient should talk to their doctor before taking NortivanCombi if:
- they have been sick (vomiting or diarrhoea),
- they have liver or kidney problems,
- they have had a kidney transplant or if they had been told to have a narrowing of the kidney arteries,
- they have a condition affecting the renal glands called "primary hyperaldosteronism",
- they have had heart failure or have experienced a heart attack. In this case they must follow your doctor's instructions for the starting dose carefully. The doctor may also check the kidney function,
- their doctor has told them 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"),
- they have experienced swelling, particularly of the face and throat, while taking other medicines (including angiotensin converting enzyme inhibitors). Those who get these symptoms, must stop taking NortivanCombi and should the doctor straight away. These patients should never take NortivanCombi again,
- 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 NortivanCombi in children and adolescents is not recommended (aged below 18 years old).

Other medicines and NortivanCombi

Patients should tell their doctor if they are taking, have recently taken or might take any other medicines. The doctor may need to change the dose and/or to take other precautions. In some cases, patients may have to stop taking one of the medicines. This applies especially to the medicines listed below:
- ACE inhibitors or aliskiren (see also information under the heading "Warnings and precautions");
- 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 patient's kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);
- St. John's wort;
- nitroglycerin 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).

NortivanCombi name} with food and drink

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

Pregnancy and breast-feeding

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

Pregnancy

Patients must tell their doctor if they think they are (or might become) pregnant. The doctor will normally advise them to stop taking NortivanCombi before a patient becomes pregnant or as soon as she knows she is pregnant and will advise her to take another medicine instead of NortivanCombi. This product is 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.

Breast-feeding

Patients should tell their doctor if they are breast-feeding or about to start breast-feeding. NortivanCombi is not recommended for mothers who are breast-feeding, and the doctor may choose another treatment for the patient if she wishes to breast-feed, especially if the baby is newborn, or was born prematurely.

Driving and using machines

This medicine may make the patients feel dizzy. This can affect how well they can concentrate. So, if patients are not sure how this medicine will affect them, they should do not drive, use machinery, or do other activities that would need them to concentrate on.

NortivanCombi contains lactose.

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

How to take NortivanCombi

This medicine should always be taken exactly as the doctor has prescribed.

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

It is important that, in case of NortivanCombi
- 5 mg/80 mg and 5 mg/160 mg film-coated tablets: the score line is only there to help to break the film-coated tablet if the patient has difficulty swallowing it whole, while

- 10 mg/160 mg film-coated tablets can be divided into equal doses.

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

Elderly (age 65 years or over)

The doctor should exercise caution when increasing their dose.

What to do if more NortivanCombi has been taken than it should have been?

If too many film-coated tablets of NortivanCombi have been taken, or if someone else has taken the patient's tablets, the doctor must be consulted immediately.

What to do if taking NortivanCombi has been forgotten?

If the patient forgets to take this medicine, he/she must 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 next dose, it is better to skip the dose that has been missed. A double dose should never be taken to make up for a forgotten tablet.

May the patient stop taking NortivanCombi?

Stopping the treatment with NortivanCombi may cause the disease to get worse. Patients should not stop taking the medicine unless the doctor tells them to.

Possible side effects

Like all medicines, NortivanCombi 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 happen, the patient must tell it the doctor 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 NortivanCombi:

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

Uncommon (may affect up to 1 in 100 people): dizziness; nausea and abdominal pain; dry mouth; loss of appetite; higher blood lipid level; elevated level of uric acid and calcium and decreased level of sodium in the blood, sore throat and discomfort when talking; drowsiness, tingling or numbness of the hands or feet; vertigo; movement coordination problems; vision impairment; fast heart beat including palpitations; dizziness on standing up possibly due to a drop in blood pressure ; 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); visual disturbance; 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 NortivanCombi or observed with a higher frequency than with NortivanCombi:

Amlodipine

Patients must consult a doctor immediately if experiencing any of the following very rare, severe side effects after taking this medicine:
- sudden wheeziness, chest pain, shortness of breath or difficulty in breathing,
- swelling of eyelids, face or lips,
- swelling of the tongue and throat which causes great difficulty breathing,
- severe skin reactions including intense skin rash, hives, reddening of the skin over the whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of the mucous membranes (Stevens-Johnson syndrome) or other allergic reactions,
- heart attack, abnormal heartbeat,
- 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 causes problems or if they last for more than one week, the patient should contact your doctor.

Common (may affect up to 1 in 10 people): dizziness, sleepiness; palpitations (awareness of your heartbeat); 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); or difficulty in breathing; indigestion, vomiting (being sick), change of bowel habit; hair loss, increased sweating, itchy skin, skin discolouration, skin rash all

over your body; sensitivity to light; 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, chest 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 brusing 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; damage to the peripheral nerves, often causes weakness, numbness and pain, usually in the hands and feet.

Not known (frequency cannot be estimated from the available data): 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; elevation of serum creatinine, decreased renal functions and severely decreased renal functions; swelling mainly of the face and the throat; muscle pain; rash, itching; inflammation of blood vessels often with skin rash, allergic reaction; blistering skin (sign of a condition called dermatitis bullous).

How to store NortivanCombi

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

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of NortivanCombi 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets. The procedure was finalised at 14 September 2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria and Romania concerned the generic version of amlodipine/valsartan fixed combinations (NortivanCombi 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets, spelt Nortivan Combi in Bulgaria).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC as amended. The reference medicinal products for these applications are Exforge 5 mg/80 mg film-coated tablets, Exforge 5 mg/160 mg film-coated tablets and Exforge 10 mg/160 mg film-coated tablets (Novartis Europharm Ltd.), authorised for marketing since 2007.

One bioequivalence study was submitted to support these applications comparing the applicant's test product with the reference product Exforge 10 mg/160 mg film-coated tablets (Novartis Europharm Limited).

With the exception of the bioequivalence study no new clinical or preclinical data, other than supporting literature, were submitted, which is acceptable for generic applications.

Amlodipine/valsartan combination combines 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.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for NortivanCombi 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets Gedeon Richter Plc.

The product is indicated for the treatment of essential hypertension. It is 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.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of NortivanCombi 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).

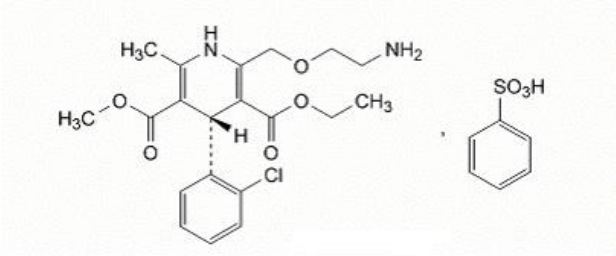
The reference products are Exforge 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets (containing 5 g or 10 mg amlodipine and 80 mg or 160 mg valsartan as active ingredients) which were the original products of Novartis.

II.2 Drug substances

II.2.1 Amlodipine besilate

Data on the quality and manufacture of the active substance were provided in the 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-di
hydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate
Structure:



and enantiomer

The drug substance is white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol. 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, additional specification has only been set for residual solvents, particle size distribution and related substances.

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 (HPLC).

Testing methods not described in detail 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 drug 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.

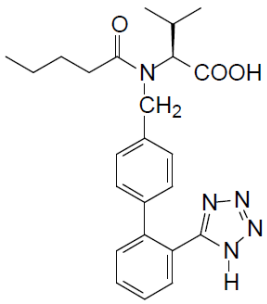
A retest period and the packaging material (polyethylene bag, in an aluminium bag kept in a PE container) have been mentioned on the CEP.

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 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 drug 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 and particle size.

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

Testing methods not described in detail 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 drug 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 LDPE bag with nitrogen purging inside a HMLDPE bag with desiccant placed in a triple poly laminated aluminium bag inside a HDPE drum) have been mentioned on the CEP.

Good Manufacturing Practice (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 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 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 product with the following appearance, composition and packaging was obtained.

- 5 mg/80 mg: round, dark yellow, biconvex film-coated tablets with bevelled edges, diameter is ~ 9 mm, with debossing 5 and 80 divided with score line. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- 5 mg/160 mg: oval, dark yellow, biconvex film-coated tablets with bevelled edges, dimensions are ~ 14.5 mm x 7.5 mm, with debossing 5 and 160 divided with score line. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- 10 mg/160 mg: oval, yellow, biconvex film-coated tablets with bevelled edges, dimensions are ~ 14.5 mm x 7.5 mm, with debossing 10 and 160 divided with score line. The film-coated tablet can be divided into equal doses.

The excipients used in the finished product are microcrystalline cellulose, maize starch pregelatinised, crospovidone Type A, sodium starch glycolate (type A), , anhydrous calcium hydrogen phosphate, anhydrous colloidal silica, magnesium stearate and film-coating (lactose monohydrate, macrogol, titanium dioxide, yellow iron oxide and hypromellose). 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 product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the 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 product is PVC/Aclar/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 no special storage conditions is approved.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality aspects the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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 none have been provided. An overview based on literature review is, thus, appropriate.

III.2 Pharmacology

NortivanCombi combines 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 combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range.

The amlodipine component of amlodipine/valsartan combination 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. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

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 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.

Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

III.3 Pharmacokinetics

Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine bioavailability is unaffected by food ingestion. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins. Amlodipine is extensively metabolised in the liver to inactive metabolites. Its elimination from plasma is bi-phasic.

Valsartan is highly bound to serum proteins, mainly serum albumin and it is not transformed to a high extent. A hydroxy metabolite has been identified in plasma at low concentrations, this metabolite is pharmacologically inactive.

Valsartan is primarily eliminated in faeces and urine, mainly as unchanged drug.

III.4 Toxicology

As for amlodipine/valsartan combinations, 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 exposures higher than the clinical doses. At even 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.

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 higher than the clinical doses. Similar changes were found in the valsartan alone group.

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at similar high exposures. There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study.

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

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since NortivanCombi 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

It has been a generic application.

Abridged applications avoid the need for repetitive tests on animals.

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 non-clinical studies are required.

From non-clinical aspects the product is approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both amlodipine and valsartan are well known. Since both compounds are widely used, well-known active substance, except for demonstrating bioequivalence, no further excessive clinical studies are required, and none have been provided. An overview based on literature review is, thus, appropriate.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Following oral administration of amlodipine/valsartan combination, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of amlodipine/valsartan are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

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. Its volume of distribution is approximately 21 l/kg.

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

IV.2.2 Bioequivalence study

In support of this applications, the applicant submitted the following bioequivalence study.

It was a pivotal, single-dose, randomized, open-label, crossover bioequivalence study under GCP conditions on the applicant's Test product Amlodipine/Valsartan 10/160 mg film-coated tablets *versus* Exforge® 10 mg/160 mg film-coated tablets (Novartis Europharm Ltd.), in healthy male subjects under fasting condition.

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

The results were as follows.

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference %	90% Confidence Intervals %	Intrasubject CV%
Amlodipine			
C_{max}	97.50	91.22 – 104.22	11.8
AUC_{0-72}	97.03	91.42 – 102.99	10.6
Valsartan			
C_{max}	109.14	98.85 – 120.51	39.8
AUC_{0-T}	102.55	94.82 – 110.92	31.1

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

Conclusion on bioequivalence study

Results derived from the analysis of log-transformed primary PK parameters (C_{max}, $AUC_{(0-T)}$ of valsartan and $AUC_{(0-72)}$ of amlodipine), namely the Test/Reference ratios of group last squares means and their 90% confidence intervals were included within the

predefined acceptance interval of 80% - 125%, as required by the *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/corr*.

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

Biowaiver for the lower strengths

The results of study with 10 mg/160 mg formulation can be extrapolated to the other strengths 5 mg/80 mg and 5 mg/160 mg, according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/corr*, section 4.1.6. since the lower strengths have fulfilled all the criteria for the biowaiver laid in the Guideline.

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

Except for those generated during the bioequivalence study 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 legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Pharmacovigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

The applicant has submitted a Risk Management Plan in accordance with the require-

ments of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to NortivanCombi 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets.

Summary of safety concerns	
Important identified risks	#1. Hyperkalaemia. #2. Hypotension. *#3.* Decreased renal function. *#4.* Foetotoxicity (with use during the 2nd or 3rd trimester of pregnancy.
Important potential risks	#5. Teratogenicity (with use during the 1st trimester of pregnancy).
Missing information	#6. Use during breastfeeding.

The summary of safety concerns is acceptable.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Richter's combination product containing amlodipine and valsartan. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, Package Leaflet, and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Richter's combination product containing amlodipine and valsartan. 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.

The application contains an adequate review of published clinical data and the bioequivalence between NortivanCombi 10 mg/160 mg film-coated tablets and Exforge® 10 mg/160 mg film-coated tablet 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.

From clinical aspects the product is approvable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Nortivan Combi 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg film-coated tablets, generic version of fix combinations of amlodipine besilate and valsartan. The applicant and the future holder of authorisation is Gedeon Richter Plc.

The products are indicated for the treatment of essential hypertension. They 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 product was are Exforge® 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets (Novartis Europharm Ltd.).

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 authorisation for Nortivan Combi 5 mg/80 mg, 5 mg/160 mg, 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 English.

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
IB C.I.3.z Changes in the product information implementing a PSUSA on amlodipine	HU/H/0473/001-003/IB/001	yes	05. 02. 2018	07. 03. 2018	approved	no
IAIN C.I.1.1.a Implementing the control strategy for N-nitrosamines according to Commission Decision C(2019) 2698	HU/H/0473/001-003/1a/002	no	24. 06. 2019	24. 07. 2019	approved	no
Withdrawal of the marketing authorisation of the 5 mg/80 mg strength in Bulgaria		yes		10. 09. 2019	approved	no