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Public Assessment Report

Name of the Product:

HU/H/0644/001-003/DC

Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/5 mg, 20 mg/10 mg tablets

(Lisinopril dihydrate/Amlodipine besilate)

Procedure number: HU/H/0644/001-003/DC

Marketing authorisation holder: Alkaloid-INT d.o.o.

Date: 29 January 2021

CONTENT

I. LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg tablets. The holder of the marketing authorisation is Alkaloid-INT d.o.o.

The active substances are lisinopril dihydrate and amlodipine besilate.

Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg tablets: each tablet contains 10 mg of lisinopril (as dihydrate) and 5 mg of amlodipine (as besilate).
Lisinopril/Amlodipine Alkaloid-INT 20 mg/10 mg tablets: Each tablet contains 20 mg of lisinopril (as dihydrate) and 10 mg of amlodipine (as besilate).
Lisinopril/Amlodipine Alkaloid-INT 20 mg/5 mg tablets: each tablet contains 20 mg of lisinopril (as dihydrate) and 5 mg of amlodipine (as besilate).

The other ingredients are: calcium hydrogen phosphate, mannitol, pregelatinised maize starch, sodium starch glycolate type A, magnesium stearate.

The appearance of the tablets is:

The 10 mg/5 mg tablets are round, white to off white, flat tablets with diameter of 8.00 ± 0.15 mm, with facet and break mark on one side, debossed with “L A” on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The 20 mg/10 mg tablets are round, white to off white, biconvex tablets with diameter of 11.00 ± 0.15 mm, with break mark on one side, debossed with “L A 2” on the other side. The tablet can be divided into equal doses.

The 20 mg/5 mg tablets round, white to off white, biconvex tablets with diameter of 11.00 ± 0.15 mm, with break mark on one side, debossed with “L A 1” on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are available in packs in blisters.

Lisinopril/Amlodipine Alkaloid-INT tablets is a combination product of amlodipine, which belongs to a group of medicines called calcium channel blockers, and lisinopril, which belongs to a group of medicines called angiotensin converting enzyme (ACE) inhibitors. Lisinopril/Amlodipine Alkaloid-INT tablets is used to treat high blood pressure (hypertension) in adults.

Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg tablets is indicated in adult patients whose blood pressure has already been controlled on a combination of 10 mg lisinopril and 5 mg amlodipine.
Lisinopril/Amlodipine Alkaloid-INT 20 mg/10 mg tablets is indicated in adult patients whose blood pressure has already been controlled on a combination of 20 mg lisinopril and 10 mg amlodipine.

Lisinopril/Amlodipine Alkaloid-INT 20 mg/5 mg tablets is indicated in adult patients whose blood pressure has already been controlled on a combination of 20 mg lisinopril and 5 mg amlodipine.

In patients with high blood pressure amlodipine works by relaxing blood vessels so that blood passes through them more easily. It also improves blood supply to the heart muscles. Lisinopril decreases the tightness of blood vessels and lowers blood pressure.

Patients might not have any symptoms from their excessively high blood pressure, but it may still increase the risk of certain complications (such as stroke or heart attack) if they do not take their antihypertensive medicine regularly.

What patients need to know before Lisinopril/Amlodipine Alkaloid-INT

Patients must not take Lisinopril/Amlodipine Alkaloid-INT if they
are allergic to lisinopril or amlodipine or any of the other ingredients of this medicine (listed in section 6).
are allergic to other ACE inhibitors (such as enalapril, captopril and ramipril) or other calcium channel blockers (such as nifedipine, felodipine or nimodipine).
have had an angioedema (severe allergic reaction, symptoms such as itching, hives, wheezing, or swelling of the hands, throat, mouth or eyelids), related or not to treatment with an ACE-inhibitor.
have a family member who has ever had a severe allergic reaction (hereditary angioedema) or if they have had a prior severe allergic reaction of unknown cause (idiopathic angioedema).
have too low blood pressure (severe hypotension).
have a narrowing of the aorta (aortic stenosis), of a heart valve (mitral stenosis) or a known abnormal thickening of the heart muscle (hypertrophic cardiomyopathy).
have circulatory failure (including cardiogenic shock).
have suffered a heart attack (myocardial infarction) with heart failure.
are more than 3 months pregnant. (Taking Lisinopril/Amlodipine Alkaloid-INT tablet in early pregnancy is not recommended either – see the "Pregnancy and breast-feeding" section).
have diabetes or impaired kidney function and they are treated with a blood pressure lowering medicine containing aliskiren.
have taken or are currently taking sacubitril/valsartan, a medicine used to treat a type of long-term (chronic) heart failure in adults, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased.

Warnings and precautions

Patients must tell their doctor if they think the are (or might become) pregnant. Lisinopril/Amlodipine Alkaloid-INT is not recommended in early pregnancy, and may cause serious harm to tehir baby if used after the 3rd months of pregnancy (see the "Pregnancy and breast-feeding" section).

Patients must talk to their doctor before taking Lisinopril/Amlodipine Alkaloid-INT if they
have heart problems
have collagen vascular disease (a connective tissue disease)
have kidney problems
have liver problems

are scheduled for surgery (including dental surgery) or anaesthesia
are under dialysis
are about to have a treatment called LDL apheresis for removal of cholesterol
are older than 65 years
are on a low-salt diet and you use potassium-containing salt substitutes or supplements or have high levels of potassium in your blood (hyperkalaemia)
have diabetes mellitus
have diarrhoea or vomiting
are on desensitisation treatment (to eliminate hypersensitivity) to reduce allergy to bee or wasp stings
are of black origin as ACE inhibitors may be less effective, but you may also more readily get angi-oedema (swelling of the face, lips, tongue and/or throat)
are taking any of the following medicines used to treat high blood pressure:
- an angiotensin II receptor blocker (ARB) (also known as sartans – for example valsar-tan, telmisartan, irbesartan), in particular if you have diabetes-related kidney disease.
- aliskiren.

are taking any medicines listed below, the risk of angioedema (sudden swelling in the area under the skin, such as in the throat) will be higher:
racecadotril, a medicine used to treat diarrhoea.
medicines used to prevent organ transplant rejection and for cancer (sirolimus, everolimus, temsirolimus and other medicines of the mTOR inhibitor class)
tissue plasminogen activators (medicines used to dissolve blood clots), generally used during hospitalization
vildagliptin, a medicine used to treat diabetes.
are taking any of the above-listed medicines (see "Other medicines and Lisinopril/Amlodipine Alkaloid-INT").

Patients must talk to their doctor if they develop a dry cough which is persistent for a long time after starting treatment Lisinopril/Amlodipine Alkaloid-INT tablet.

The doctor may check the patient's blood pressure, kidney function with a blood test and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

Children and adolescents

Lisinopril/Amlodipine Alkaloid-INT should not be used in children below 18 years of age.

Other medicines and Lisinopril/Amlodipine Alkaloid-INT

Those who are taking, have recently taken or might take any other medicines must consult their doctor.

Potassium-sparing diuretics (such as spironolactone, amiloride, triamterene, used to reduce fluid retention) and potassium-containing salt substitutes or potassium supplements or may only be taken together with Lisinopril/Amlodipine Alkaloid-INT tablet under close medical supervision.

Special caution is necessary when Lisinopril/Amlodipine Alkaloid-INT tablet is taken together with the following medicines:
water tablets (used to reduce fluid retention)

other medicines used to lower blood pressure (antihypertensives)
medicines used in the treatment of heart diseases (e.g. verapamil, diltiazem)
non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (used to alleviate joint inflammation, muscle pain, headache, inflammation, fever)
lithium, tricyclic antidepressants, antipsychotics (used to treat mental disorders)
insulin and oral antidiabetics (medicines used to treat high blood glucose levels)
autonomous nervous system stimulants (sympathomimetics), such as ephedrine, phenylephrine, xylometazoline and salbutamol (used to treat congestion, cough, cold and asthma)
immunosuppressants (used to prevent transplant rejection, e.g. corticosteroids, cytotoxic agents and antimetabolites)
allopurinol (used to treat gout)
procainamide (used to treat arrhythmias)
potassium supplements (including salt substitutes), potassium-sparing diuretics and other medicines that increase the amount of potassium in your blood (e.g. trimethoprim and co-trimoxazole for infections caused by bacteria; ciclosporin, an immunosuppressant medicine used to prevent organ transplant rejection; heparin a medicine used to thin blood to prevent clots)
simvastatin (used to lower cholesterol and blood fat levels)
narcotics, morphine and related drugs used (to treat severe pain)
anticancer medicines
- anaesthetics, used in surgery or some dental procedures. Patients should consult their doctor or dentist that they are taking Lisinopril/Amlodipine Alkaloid-INT tablet before they are given a local or general anaesthetic, as there is a risk of a sudden transient drop in blood pressure.
anticonvulsants (such as carbamazepine, phenobarbital and phenytoin) – used to treat epilepsy
medicines for the treatment of bacterial (antibiotics e.g. rifampicin, erythromycin or clarithromycin), HIV (so-called protease inhibitors e.g. ritonavir, indinavir, nelfinavir) or fungal infections (e.g. ketoconazole, itraconazole)
herbal remedies containing St. John's wort (*Hypericum perforatum*)
gold salts, especially when given intravenously (used to treat the symptoms of rheumatoid arthritis)
dantrolene (a skeletal muscle relaxant used to treat high body temperature [malignant hyperthermia] caused by hypnotic agents used during surgery)
tacrolimus (used to regulate the body's immune response to help the body accept the transplanted organ)

The following medicines may increase the risk of angioedema (signs of angioedema may include swelling of the face, lips, tongue and/or throat with difficulty swallowing or breathing):
medicines used to dissolve blood clots (tissue plasminogen activators), generally used during hospitalization.
medicines most often used to prevent organ rejection following organ transplant and for cancer (sirolimus, everolimus, temsirolimus and other mTOR inhibitors). See "Warnings and precautions".
vildagliptin, a medicine used to treat diabetes.
racecadotril, used to treat diarrhoea.

Patients' doctor may need to change their dose and/or to take other precautions:
if they are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also the information under the headings "Do not take Lisinopril/Amlodipine Alkaloid-INT" and "Warnings and precautions").

Lisinopril/Amlodipine Alkaloid-INT with food and drink

Lisinopril/Amlodipine Alkaloid-INT tablet can be taken with or without food, but alcohol should be avoided during treatment. Grapefruit juice and grapefruit should not be consumed while taking Lisinopril/Amlodipine Alkaloid-INT. This is because the consumption of 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 Lisinopril/Amlodipine Alkaloid-INT.

Pregnancy and breast-feeding

Pregnancy

Patients must tell their doctor if they think they are or might become pregnant. Their doctor will normally advise them to stop taking Lisinopril/Amlodipine Alkaloid-INT before they become pregnant or as soon as they know they are pregnant and will recommend another medicine instead of Lisinopril/Amlodipine Alkaloid-INT. Lisinopril/Amlodipine Alkaloid-INT is not recommended in early pregnancy, and must not be taken if patients are more than 3 months pregnant, as it may cause serious harm to the foetus.

Breast-feeding

Amlodipine has been shown to be excreted into breast milk in small amounts. Patients must tell their doctor if they are breast-feeding or about to start breast-feeding. Lisinopril/Amlodipine Alkaloid-INT is not recommended for mothers who are breast-feeding. Their doctor will probably recommend another medicine for them if they wish to breast-feed, especially if their baby is newborn or was born prematurely.

Driving and using machines

Before driving a vehicle or operating machines, or carrying out other activities that require concentration, patients must make sure they know how Lisinopril/Amlodipine Alkaloid-INT affects them.
Lisinopril/Amlodipine Alkaloid-INT can affect their ability to drive and use machinery safely (especially at the start of the treatment).
Patients shoud not drive or use machines if they notice Lisinopril/Amlodipine Alkaloid-INT negatively affect their ability to drive or operate machines, e.g. makes them feel sick, dizzy or tired, or gives them a headache.

How to take Lisinopril/Amlodipine Alkaloid-INT

Patients should always take this medicine exactly as their doctor has told them. If they are not sure, their doctor or pharmacist must be checked with.
The recommended dose is one tablet of Lisinopril/Amlodipine Alkaloid-INT daily.
Lisinopril/Amlodipine Alkaloid-INT tablet can be taken with or without food.
Each tablet should be swallowed whole with a small amount of water. Tablet should be taken at the same time each day.

The score line on the 10 mg/5 mg tablets is only there to help patients break the tablet if they have difficulty swallowing it whole.
The score line on the 20 mg/5 mg tablets is only there to help patients break the tablet if they have difficulty swallowing it whole.
Lisinopril/Amlodipine Alkaloid-INT 20 mg/10 mg tablet can be divided into equal doses.

If patients feel that the effect of Lisinopril/Amlodipine Alkaloid-INT is too strong or too weak, they should talk to their doctor or pharmacist.

Use in children and adolescents

Lisinopril/Amlodipine Alkaloid-INT should not be used in children below age 18 due to lack of data on safety and efficacy.

Elderly
Generally no special dosage modification is necessary in patients over the age of 65.

Liver impairment
Liver disease can influence the blood level of amlodipine. In this case patients' doctor will advise more frequent checking.

Kidney impairment
Regular monitoring of renal function, serum potassium and sodium levels is required during therapy with Lisinopril/Amlodipine Alkaloid-INT tablets. In case of worsening of the kidney function Lisinopril/Amlodipine Alkaloid-INT will be withdrawn and replaced by therapy with the individual components adequately adjusted.

What to do if more Lisinopril/Amlodipine Alkaloid-INT was taken that it should have been?

The doctor or the nearest hospital emergency department must be contacted immediately. Lisinopril/Amlodipine Alkaloid-INT overdose is likely to result in very low blood pressure, which has to be closely monitored. Signs of an overdose are electrolyte disorders, kidney failure, rapid breathing (hyperventilation), a fast heart beat, palpitations, a slow heart beat, dizziness, anxiety and cough. Patients may feel dizzy, faint or feel weak. Shock may also occur in the event of a severe drop in blood pressure. Their skin may feel cold and clammy and they may lose consciousness. If characteristic symptoms (such as dizziness and headache) occur, patients should be placed lying down with the face up. Their doctor will take further measures.

What to do if taking Lisinopril/Amlodipine Alkaloid-INT was forgotten?

No double dose to make up for a forgotten tablet must be taken, in order to avoid the risk of overdose. Next dose must be taken at the usual time.

May patients stop taking Lisinopril/Amlodipine Alkaloid-INT?

The duration of treatment will be determined by patients' doctor. Taking the tablets must not be stopped even if patients feel better. If they stop taking the medicine earlier than

recommended, their condition may get worse.

If patients have any further questions on the use of this medicine, their doctor or pharmacist should be asked.

Possible side effects

Like all medicines, Lisinopril/Amlodipine Alkaloid-INT can cause side effects, although not everybody experiences them.

Common side effects (may affect up to 1 in 10 patients):
In a clinical trial with a combination of amlodipine and lisinopril, common side effects were: headache, cough and dizziness.

Allergic (hypersensitivity) reactions may occur with the use of Lisinopril/Amlodipine Alkaloid-INT. Patients must stop taking Lisinopril/Amlodipine Alkaloid-INT and seek medical attention immediately if they develop any of the following symptoms of *angioedema:*
- difficulty breathing with or without swelling of the face, lips, tongue and/or throat.
- swelling of the face, lips, tongue and/or throat which may cause difficulty swallowing.
- severe skin reactions, including pronounced rash, hives, reddening of the skin on the entire body, severe itching, blistering, peeling and swelling of the skin, inflammation of the mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis) or other allergic reactions.

Additional side effects that have been reported with either amlodipine or lisinopril alone (the two active substances) that may also occur with Lisinopril/Amlodipine Alkaloid-INT are:

Amlodipine

Very common side effects (may affect more than 1 in 10 patients)
Oedema.

Common side effects (may affect up to 1 in 10 patients)
Headache, ankle swelling, muscle cramps, fatigue, weakness, somnolence, visual disturbances, nausea, indigestion, altered bowel movements (diarrhoea and constipation), dizziness, abdominal pain, palpitations (a quicker or irregular heartbeat), flushing, difficulty breathing.
Patients must contact their doctor if these side effects cause them any problems or if they persist for more than one week.

Uncommon side effects (may affect up to 1 in 100 patients)
Skin rash, itching skin, hair loss, red patches on the skin, skin discolouration, hives, vomiting, muscle or joint pain, back pain, chest pain, mood changes (including anxiety), depression, sleeplessness, tremor, ringing in the ear, irregular heart beat (arrhythmia), low blood pressure, cough, disturbances in taste, sensation disturbances (numbness or tingling sensation), runny nose, frequent need to urinate at night, urination disorders, dry mouth, absence of pain sensation, increased sweating, fainting, pain, malaise, enlargement of breasts in men, impotence,

weight gain, weight loss.

Rare side effects (may affect up to 1 in 1,000 patients)
Confusion.

Very rare side effects (may affect up to 1 in 10,000 patients)
Allergic reactions, abnormal liver function tests, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), decrease in the number of white blood cells and platelets, elevation of blood glucose, heart attack (myocardial infarction), severe skin reactions (skin rash, scaly or peeling skin), severe allergic reactions accompanied by fever, red patches, joint pain and/or eye disorders (Stevens-Johnson syndrome), swelling or ulceration of the gums, inflammation of the pancreas, inflammation of the lining of the stomach, photosensitivity, increased muscle tension, peripheral neuropathy (nervous system disorder: weakness and tingling sensation), inflammation of blood vessels.

Not known (frequency cannot be estimated from the available data)
Tremor, stilted posture, mask-like face, slow movements and shuffling, unbalanced gait.

Lisinopril

Common side effects (may affect up to 1 in 10 patients)
Headache, dizziness or light-headedness – especially when standing up quickly, diarrhoea, cough, vomiting, kidney problems.

Uncommon side effects (may affect up to 1 in 100 patients)
Mood changes, change of colour (pale blue followed by redness) and/or numbness or tingling in the fingers or toes (Raynaud's phenomenon), altered taste perception, hallucinations (seeing things that are not real), fatigue, feeling sleepy or difficulty in going to sleep, spinning feeling, paraesthesia (tingling, itching, burning), rapid and irregular heartbeat (palpitations), heart attack (myocardial infarction), stroke, runny nose, nausea, stomach pain or indigestion, impotence, tiredness, changes in the results of certain laboratory tests (that show how your kidney and liver are working), skin rash, itching, rapid heartbeat (tachycardia).

Rare side effects (may affect up to 1 in 1,000 patients)
Angioedema (hypersensitivity reaction with sudden swelling of the lips, face and neck, and occasionally of the feet and hands – there is a higher rate of angioedema in black patients than in nonblack patients). Confusion, inappropriate secretion of the antidiuretic hormone, which controls the amount of urine, acute kidney problems, kidney failure, dry mouth, hair loss, psoriasis, hives, enlargement of breasts in men. Smell perception disorder.
Worsening of blood count: decrease in haemoglobin and haematocrit levels. Increase in bile pigment (bilirubin) level, low level of sodium in the blood.

Very rare side effects (may affect up to 1 in 10,000 patients)
Decrease of blood glucose (hypoglycaemia), sinus pain, wheezing, pneumonia, yellow discolouration of the skin and/or eyes (jaundice), inflammation of the liver or pancreas, liver failure, severe skin disorders (symptoms of which include redness, blistering and peeling), sweating.
Significant reduction of urine volume (or absence of urine). Swelling of the bowels.

Deterioration of blood cells: decrease in the number of red blood cells (anaemia), decrease in the number of platelets (thrombocytopenia), decrease in the number of white blood cells (neutropenia, leukopenia, agranulocytosis). These problems may cause prolonged bleeding, tiredness, weakness, disease of the lymph nodes, autoimmune disorder (when your immune system turns against itself). Patients can get infections more easily.

Not known (frequency cannot be estimated from the available data)
Fainting, depression, severe allergic hypersensitive reaction (anaphylactic/anaphylactoid reaction).

How to store Lisinopril/Amlodipine Alkaloid-INT?

This medicine does not require any special temperature storage conditions. It should be stored in the original package in order to protect from light and 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 the Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg tablets. The procedure was finalised at 26 August 2020. For information on changes after this date please refer to the module 'Update'.

II. 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, Croatia, Malta, Poland, Portugal, Slovenia) concerned the generic version of lisinopril dihydrate/amlodipine besilate 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg.

Based on the review of the quality, safety and efficacy data, the Member States have granted the marketing authorisation for Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg tablets from Alkaloid-INT d.o.o.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic application).

To support the application, the Applicant has submitted two pivotal bioequivalence studies. The reference products used in the bioequivalence studies were Dironorm 20 mg/10 mg and 20 mg/5 mg of GEDEON RICHTER POLSKA Sp. z o.o.

Treatment of essential hypertension in adults.
The Product is indicated as substitution therapy of adult patients with blood pressure adequately controlled with lisinopril and amlodipine given concurrently at the same dose level.

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

III. QUALITY ASPECTS

III.1 Introduction

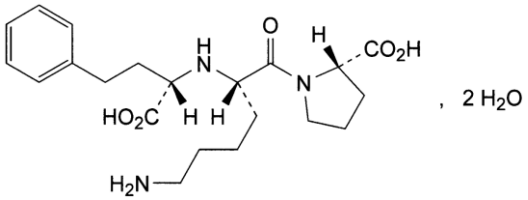
The chemical-pharmaceutical assessment report concerns the application of Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e a generic application). The product has been developed by Alkaloid AD, Skopje.
Reference products are Dironorm® 20 mg/5 mg and 20 mg/10 mg tablets (containing 20 mg Lisinopril and 5 mg or 10 mg amlodipine as active ingredients, respectively) which were the original products of Gedeon Richter Plc.

III.2 Drug substances

III.2.1 Lisinopril dihydrate

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

INN name: Lisinopril dihydrate
Chemical name: L-Proline, 1-[N2- (1-carboxy-3-phenylpropyl)-L-lysyl]-, dihydrate, (S)-1-[N2- [(S)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate
Structure:



The active substance is white or almost white, crystalline powder; soluble in water, practically insoluble in anhydrous ethanol and in heptane. It shows polymorphism, the manufacturers consistently produce the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph.Eur. (European Pharmacopoeia) monograph and supplemented with additional tests specified in the respective CEPs and DMF of the API manufacturer(s).
The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

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

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

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

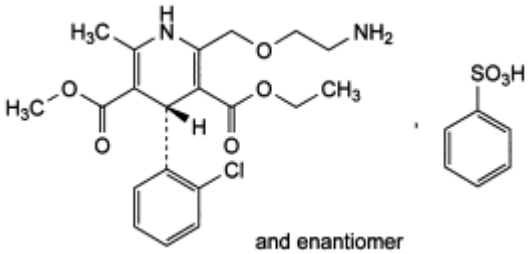
Stability studies have been performed with the drug substance or a retest period and the packaging material have been mentioned on the CEP.

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

III.2.2 Amlodipine besilate

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

INN name: Amlodipine besilate
Chemical name: 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylatebenzenesulphonate
Structure:



The active substance is white or almost white powder; slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol. It shows polymorphism, the manufacturers consistently produce the same polymorphic form.

The substance is specified according to the requirements of the current Ph.Eur. monograph and supplemented with additional tests specified in the respective CEPs and DMF of the API manufacturer(s). The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug product manufacturer for the control of the substance are adequately characterized.
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 have been mentioned on the CEPs.

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

III.3 Medicinal product

The aim was to develop tablets containing lisinopril and amlodipine as drug substances in 10 mg/5 mg, 20 mg/5 mg and 20 mg/10 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal products (Dironorm® 20 mg/10 mg, 10 mg/5 mg and 20 mg/5 mg tablets), the original products of Gedeon Richter Plc.

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 products with the following appearance and composition were obtained.
10 mg/5 mg tablets: Round, white to off white, flat tablets with diameter of 8.00 ± 0.15 mm, with facet and break mark on one side, debossed with “L A” on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
20 mg/10 mg tablets: Round, white to off white, biconvex tablets with diameter of 11.00 ± 0.15 mm, with break mark on one side, debossed with “L A 2” on the other side. The tablet can be divided into equal doses.
20 mg/5 mg tablets: Round, white to off white, biconvex tablets with diameter of 11.00 ± 0.15 mm, with break mark on one side, debossed with “L A 1” on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The excipients used in the finished product are calcium hydrogen phosphate, mannitol, pregelatinised maize starch, sodium starch glycolate (type A) and magnesium stearate. 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 product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form

monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence studies are presented.

The container closure system of the product is PVC/PVdC//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 2 years is approved with the following storage restriction: “Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions.”

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

III.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: 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.

IV. NON-CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of lisinopril and amlodipine are well known. As lisinopril and amlodipine are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required.

Overview based on literature review is appropriate.

IV.2 Pharmacology

Lisinopril inhibits the angiotensin-converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II.
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

IV.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

IV.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

IV.5 Ecotoxicology/environmental risk assessment

Since Lisinopril/Amlodipine Alkaloid-INT 20 mg/5 mg, 10 mg/5 mg and 20 mg/10 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.

IV.6 DISCUSSION ON THE NON-CLINICAL ASPECTS

Abridged applications avoid the need for repetitive tests on animals. Pharmacodynamic, pharmacokinetic and toxicological properties of lisinopril and amlodipine are well known. The non-clinical part of the application is acceptable.

V. CLINICAL ASPECTS

V.1 INTRODUCTION

Pharmacodynamics, pharmacokinetics, efficacy and safety of lisinopril and amlodipine are well established.

To support the application, the Applicant submitted two pivotal bioequivalence studies.

The application contains an adequate review of published clinical data.

V.2 Pharmacokinetics

Lisinopril

Lisinopril is an orally active non-sulfhydryl-containing ACE inhibitor.

Absorption
Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25% with inter-patient variability of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Distribution
Lisinopril does not appear to be bound to serum proteins other than to circulating ACE. Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination
Lisinopril does not undergo metabolism and is excreted unchanged into the urine. On multiple dosing, lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Amlodipine

Absorption, distribution and plasma protein binding
After oral administration amlodipine is well absorbed, producing peak plasma concentrations between 6-12 hours post dose. Absolute bioavailability is between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The bioavailability of amlodipine is not affected by food intake.

Biotransformation and elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Bioequivalence studies

The applicant submitted the request for Marketing Authorisations of Lisinopril/Amlodipine Alkaloid-INT 20 mg/5 mg, 10 mg/5 mg and 20 mg/10 film-coated tablets. To support the application, the Applicant has submitted as report two pivotal single-dose bioequivalence studies (study No 2286 and 2352).

One pivotal bioequivalence study (study No 2286) has been reported in the submitted Dossier in order to support essential similarity between Lisinopril/Amlodipine 20 mg/10 mg (Manufactured By: Alkaloid AD Skopje) single oral dose and Dironorm (Lisinopril/Amlodipine) 20 mg/10 mg Tablets (Manufactured By: Gedeon Richter Plc.; MAH: GEDEON RICHTER POLSKA Sp. z o.o). single oral dose in healthy volunteers under fasting conditions.

A second pivotal bioequivalence study (study No 2352) has been reported in the submitted Dossier in order to support essential similarity between Lisinopril/Amlodipine 20 mg/5 mg (Manufactured By: Alkaloid AD Skopje) single oral dose and Dironorm (Lisinopril/Amlodipine) 20 mg/5 mg Tablets (Manufactured By: Gedeon Richter Plc.; MAH: GEDEON RICHTER POLSKA Sp. z o.o). single oral dose in healthy volunteers under fasting conditions.

By the Sponsor's statement the two bioavailability studies (2286 & 2352) were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with Harmonized Tripartite Guidelines for Good Clinical Practice and according to principles of Good Laboratory Practice (GLP) respectively.

Bioequivalence study No. 2286

The study was designed as an open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-centre, single dose, crossover bioequivalence study under fasting condition which included 50 healthy subjects with 21 days washout period.

Criteria for Bioequivalence:

To establish bioequivalence, the calculated 90% CI for the ratio of geometric means for AUC_{72} and C_{max} for amlodipine, and the ratio of geometric means for AUC_t, AUC_{inf} and C_{max} for lisinopril should fall within 80.00%-125.00%.

Table 3.3A Bioequivalence Evaluation of Amlodipine in 2286

Pharmacokinetic parameter	Geometric Mean Ratio Test / Reference	Confidence Intervals	CV%
AUC_{72}	100.49	98.14 – 102.89	6.90
C_{max}	104.48	100.42 – 108.71	11.61

Table 3.3B Bioequivalence Evaluation of Lisinopril in 2286

Pharmacokinetic parameter	Geometric Mean Ratio Test / Reference	Confidence Intervals	CV%
AUC_t	103.00	96.02 – 110.48	20.67
AUC_{inf}	102.61	95.96 – 109.73	19.74
C_{max}	104.36	96.47 – 112.90	23.24

Bioequivalence study No. 2352

The study was designed as an open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-centre, single dose, crossover bioequivalence study under fasting condition which included 50 healthy subjects with 21 days washout period.

Criteria for Bioequivalence:

To establish bioequivalence, the calculated 90% CI for the ratio of geometric means for AUC_{72} and C_{max} for amlodipine, and the ratio of geometric means for AUC_t, AUC_{inf} and C_{max} for lisinopril should fall within 80.00%-125.00%.

Table 3.3A Bioequivalence Evaluation of Amlodipine in 2352

Pharmacokinetic parameter	Geometric Mean Ratio Test / Reference	Confidence Intervals	CV%
AUC_{72}	99.13	96.64 – 101.68	7.50
C_{max}	100.23	97.19 – 103.37	9.11

Table 3.3B Bioequivalence Evaluation of Lisinopril in 2352

Pharmacokinetic parameter	Geometric Mean Ratio Test / Reference	Confidence Intervals	CV%
AUC_t	95.61	88.84 – 102.90	21.93
AUC_{inf}	96.00	89.35 – 103.13	21.39
C_{max}	96.32	89.03 – 104.21	23.52

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence studies Amlodipine/Lisinopril 10 mg/20 mg Tablets (Manufactured By: Alkaloid AD Skopje) is considered bioequivalent with Dironorm (Amlodipine/Lisinopril) 10 mg/20 mg Tablets (Manufactured By: Gedeon Richter Plc.; MAH: GEDEON RICHTER POLSKA Sp. z o.o).

Based on the submitted bioequivalence studies Lisinopril/Amlodipine 20 mg/5 mg Tablets (Manufactured By: Alkaloid AD Skopje) is considered bioequivalent with Dironorm (Lisinopril/Amlodipine) 20 mg/5 mg Tablets (Manufactured By: Gedeon Richter Plc.; MAH: GEDEON RICHTER POLSKA Sp. z o.o).

Biowaiver

The Applicant requested a biowaiver to the 10 mg/5 mg Lisinopril/Amlodipine combination.
A waiver for additional strengths is claimed in accordance with the European Medicines Agency (EMA) Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1 Corr **, since the general biowaiver requirements are met. *In vitro* dissolution profiles, qualitative and quantitative composition justified biowaiver request for 10 mg/5 mg strength of lisinopril/amlodipine.

V.3 Pharmacodynamics

Lisinopril
Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Amlodipine

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

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 amlodipine administration.

V.4 Clinical efficacy

Clinical efficacy of lisinopril and amlodipine is well-established. No new efficacy study was performed which is acceptable for this type of application. The Applicant has provided an adequate literature review.

V.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

The Applicant has provided an adequate literature review.

V.6 Pharmacovigilance

V.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 GVP module, the Summary is considered acceptable.

V.6.2 Risk Management Plan

The MAH has submitted a risk management plan (version 0.6, dated 17.08.2020) in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/5 mg and 20 mg/10 film-coated tablets.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

According to the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) 28 March 2017 EMA/838713/2011 Rev 2*) only those important identified or potential risks and missing information should be presented which are linked to further PV activities or additional risk minimization measures in the EU.

Considering, that Lisinopril-Amlodipine fix-combination has been used in the proposed indication for a long period of time, all risks are well known and there is no need for additional pharmacovigilance activities. The SmPC and PIL contains sufficient information regarding the preventability of risks and minimisation thereof, there is no need for additional risk minimisation measures. Risks requiring medical attention or monitoring have become part of everyday practice. Considering the above, the list of safety concerns has been kept empty.

IV.6.3 Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to ALKALOID-INT’s combination product containing lisinopril and amlodipine.

No additional activities are proposed.

V.6.3 Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to ALKALOID-INT's combination product containing lisinopril and amlodipine.
No additional risk minimisation measures are proposed. For any further information on risk minimisation, please refer to the product information.

V.6.4 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.

V.7 Discussion on the clinical aspects

The applications concern generic products and for this type of applications the bioequivalence studies are pivotal. The Applicant has adequately demonstrated bioequivalence between Lisinopril/Amlodipine Alkaloid-INT 20 mg/5 mg, 10 mg/5 mg and 20 mg/10 tablets and the reference products Dironorm 20 mg/10 mg and 20 mg/5 mg (GEDEON RICHTER POLSKA Sp. z o.o).

The application contains an adequate review of published clinical data.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

VI.1 Summary

The present applications concern Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg, generic version of lisinopril dihydrate/amlodipine besilate 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg. The applicant and the future holder of authorisation is Alkaloid-INT d.o.o.

Treatment of essential hypertension in adults.
The product is indicated as substitution therapy of adult patients with blood pressure adequately controlled with lisinopril and amlodipine given concurrently at the same dose level.

The application for this generic product contains an adequate review of published non-clinical and clinical data. Moreover, to support the application the applicant demonstrated bioequivalence between the generic products and the marketed "reference" product (Dironorm 20 mg/10 mg and 20 mg/5 mg) that contained the active components of the combination in corresponding strengths: lisinopril dihydrate/amlodipine besilate.

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 the marketing authorisation for Lisinopril/Amlodipine Alkaloid-INT 10 mg/5 mg, 20 mg/10 mg, 20 mg/5 mg tablets from Alkaloid-INT d.o.o.

VI.2 Classification

Prescription-only medicine.

VI.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a bridging study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

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.

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VII. 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