GYEMSZI
Gyógyszerészeti és Egészségügyi
Minőség- és Szervezetfejlesztési Intézet

Public Assessment Report

Name of the Product:

Atorvastatin/Amlodipin Richter 10/5 mg, 20/5 mg and 20/10 mg

Lidorat 10/5 /10 mg

Torviman 10/5, 20/5 and 20/10 mg

film-coated tablets

(atorvastatin/amlodipine)

Procedure numbers:
HU/H/0320/001, 003, 004/DC
HU/H/0321/001, 003, 004/DC
HU/H/0322/001, 003, 004/DC

Marketing authorisation holder in the RMS: Gedeon Richter Plc.

Date: 4 June 2013

CONTENT

LAY SUMMARY

After careful assessment of their quality and therapeutic benefit/risk ratio, the member states authorised for marketing the fixed combinations of atorvastatin as (lysine salt)/amlodipine (as besylate) 10 mg/5 mg, 20 mg/5 mg and 20 mg/10 mg under the names of Atorvastatin/Amlodopin Richter, Lidorat and Torviman (multiple, i.e. copy applications).

The other ingredients are:

- *tablet core:* calcium carbonate, cellulose microcrystalline, starch, pregelatinised (maize), croscarmellose sodium, calcium oxide, sodium starch glycolate type A, hydroxypropylcellulose, polysorbate 80, colloidal anhydrous silica, magnesium stearate;
- *tablet coating:* poly(vinyl alcohol), partially hydrolyzed, titanium dioxide (E171), macrogol 3350, talc.

The appearances of the medicinal products are as follows:

- the 10 mg/5 mg film-coated tablets are white, round, biconvex. Engraving on one side: “CE3”, the other side is without engraving,
- the 20 mg/5 mg film-coated tablets are white, oblong, biconvex. Engraving on one side: “CE4”, the other side is without engraving,
- the 20 mg/10 mg film-coated tablets are white, oblong, biconvex. Engraving on one side: “CE6”, the other side is without engraving.

Atorvastatin belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

Amlodipine belongs to a group of medicines called calcium antagonists, they work by relaxing blood vessels.

The combination products are indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease and/or Prinzmetal’s angina) in adult patients with one of the following coincident conditions:

- elevated cholesterol levels (called primary hypercholesterolaemia), or elevated cholesterol and triglyceride levels at the same time (called combined or mixed hyperlipidaemia).
- elevated cholesterol levels of hereditary origin (called homozygous familial hypercholesterolaemia).
- need of prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

These combination products are not intended for initial therapy. Taking the components (medicinal products that contain atorvastatin and amlodipine) should be stopped when start taking the combination product. Moreover, a standard cholesterol lowering diet during treatment should be maintained.

What one needs to know before taking this combination

Do not take it

- if you are allergic to amlodipine or to atorvastatin, or if you are allergic to a group of substances called “calcium channel blockers” or to any similar medicines to atorvastatin used to lower blood lipids, or any of the other ingredients of this medicine,
- if you have severe low blood pressure (hypotension).
- if you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- if you suffer from heart failure after a heart attack.
- if you have or have ever had a disease which affects the liver.
- if you have had any unexplained abnormal blood tests for liver function.
- if you are pregnant or trying to become pregnant.
- if you are a woman able to have children and not using reliable contraception.
- if you are breast-feeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking it:

- if you have heart failure.
- if you recently had a heart attack.
- if you have severe increase in your blood pressure (hypertensive crisis).
- if you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes.
- if you have kidney problems.
- if you have an under-active thyroid gland (hypothyroidism).
- if you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems.
- if you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other ‘-statin’ or ‘-fibrate’ medicines).
- if you regularly drink a large amount of alcohol.
- if you have a history of liver disease.
- if you are older than 70 years.

Check with your doctor or pharmacist before taking this combination if you have severe respiratory failure.

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your combination treatment to predict your risk of muscle related side effects. The risk of muscle related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time.

Take special care with this combination, if you have diabetes.

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

Children and adolescents: this combination is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Other medicines and the atorvastatin/amlodipine combination

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There are some medicines that may change the effect of this combination or their effect may be changed by it. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side-effects, including the important muscle wasting condition known as rhabdomyolysis (described above).

- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid,
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, colestipol.
- Some calcium channel blockers used for angina or high blood pressure, e.g. diltiazem; medicines to regulate your heart rhythm e.g. digoxin, verapamil, amiodarone.
- Medicines used to alter the way your immune system works, e.g. cyclosporine.
- Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, nelfinavir, etc.
- Other medicines known to interact with {(Invented) name} include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stiripentol (an anti-convulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazone (a painkiller) and antacids (indigestion products containing aluminium or magnesium).
- Dantrolene (infusion for severe body temperature abnormalities).
- Medicines obtained without a prescription: St. John's Worth (Hypericum perforatum).

This combination may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

The atorvastatin/amlodipine combination with food and drink and alcohol

It may be taken with or without food.

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

Avoid drinking too much alcohol while taking this medicine.

Pregnancy and breast-feeding

Do not take the atorvastatin/amlodipine combination if you are pregnant, or if you are trying to become pregnant. Do not take is if you are able to become pregnant unless you use reliable contraceptive measures.

Do not take it if you are breast-feeding.

The reason is that the safety of this combination during pregnancy and breast-feeding has not been proven. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Normally this medicine does not affect your ability to drive or operate machines. However, do not drive or use machines if the tablets make you feel sick, dizzy or tired, or give you a headache or blurred vision, or affects your ability to drive and use machines in any other way.

How to take the atorvastatin/amlodipine combinaton

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with {(Invented) name}.

Adults

The dose of this combination as determined by the doctor can be one 10 mg/5 mg or one 20 mg/5 mg or one 20 mg/10 mg film-coated tablet per day. The maximum daily dose is one 20 mg/10 mg film-coated tablet.

Swallow each tablet whole with a drink of water. You can take it at any time of the day with or without food. Try to take your tablet at the same time every day.

Follow the dietary advice of the doctor particularly about the low-fat diet; do physical exercises regularly and do not smoke.

The duration of treatment is determined by your doctor.

There is no need to modify the dose for elderly patients.

Dose change is not necessary in these patients with kidney impairment.

Use in children and adolescents is not recommended.

Patients with liver impairment: this combination should be administered with caution in these patients and regular medical follow-up should include frequent monitoring of liver function.

If you take more film-coated tablets of these combinations than you should

Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. If you have taken more combination coated tablets than you should have, immediately contact your doctor or the nearest hospital for advice. Take along any tablets that are left, the container and the label so that the hospital can easily tell what medicine you have taken.

If you forget to take a dose of these combination film-coated tablets

If you forget to take a dose, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

Do not stop taking your medicine unless your doctor tells you to do so.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you experience any of the following serious side effects, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.

Common (may affect up to 1 in 10 people)

- drowsiness, headache, dizziness (especially at the beginning of the treatment), tiredness,
- inflammation of the nasal passages, pain in the throat, nose bleed,
- flushing,
- palpitations (awareness of your heartbeat),
- abdominal pain, feeling sick (nausea), constipation, wind, indigestion, diarrhoea,
- muscle pain, muscle cramps, ankle oedema/swelling, joint pain and back pain, pain in extremities,
- allergic reactions,
- oedema,
- increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels),
- increase in blood creatine kinase,
- blood test results that show your liver function can become abnormal.Uncommon (may affect up to 1 in 100 people):
- inflammation of the lining of the nose (rhinitis/sneezing, running nose),
- anorexia (loss of appetite), weight gain, weight decrease, decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels),
- change of mood, anxiety, depression, trembling,
- numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory,
- visual disturbances (including double vision), blurred vision,
- ringing in the ears and/or head,
- chest pain,
- breathlessness, faint, low blood pressure (hypotension),
- dry mouth, vomiting, belching, pancreatitis (inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell),
- hepatitis (liver inflammation),
- hair loss, red patches on skin, discoloration of the skin, rash, skin rash and itching, hives, exanthema, increased sweating,
- neck pain, muscle fatigue, weakness,
- disorder in passing urine, increased need to urinate at night, increased number of times of passing urine,

- inability to obtain an erection (impotence), gynecomastia (discomfort or enlargement of the breasts in men),
- raised temperature, feeling unwell, pain, peripheral oedema/swelling,
- having nightmares, insomnia,
- urine tests what are positive for white blood cells.

Rare (may affect up to 1 in 1000 people):
- serious allergic reaction which causes swelling of the face, tongue and throat, that can cause great difficulty in breathing,
- serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes genitals and fever. Skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister,
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown (rhabdomyolysis), which can be life-threatening and lead to kidney problems,
- decrease in blood platelets which may result in unexpected bleeding or bruising ,
- cholestasis (yellowing of the skin and whites of the eyes),
- confusion,
- peripheral neuropathy (a disorder of the nerves which can cause weakness, tingling or numbness),
- tendon injury,
- angioedema.

Very rare (may affect up to 1 in 10 000 people):
- heart attack, abnormal heartbeat,
- if you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible.
- decrease of white blood cells in the blood,
- muscle stiffness or muscle tension, disorders combining rigidity, tremor, and/or movement disorders,
- arrhythmias, heart attack, inflammation of the small blood vessels,
- increased growth of gum,
- cough,
- an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse,
- photosensitivity,
- hearing loss,
- abdominal bloating (gastritis),
- hepatic failure.

Other possible side effects reported with some statins (medicines of the same type):
- sexual difficulties,
- depression,
- breathing problems including persistent cough and/or shortness of breath or fever,
- diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

How to store the atorvastatin/amlodipine combonation film-coated tablets

Store them below 25°C. Store in the original package in order to protect from light and moisture.

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

Scientific discussion

This module reflects the scientific discussion for the approval of Atorvastatin/Amlodipin Richter, Lidorat and Torviman 10 mg/5 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets. The procedure was finalised at 25. 06. 2012. 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*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, a multiple (copy) application for marketing authorisation of Lidorat, Atorvastatin/Amlodipine Richter and Torviman film-coated tablets 10 mg/5 mg. 20 mg/5 mg and 20 mg/10 mg atorvastatin L-lysine/amlodipine besylate has been submitted to the reference and competent authorities of the Member State concerned.

The reference member state (RMS) was Hungary. The concerned member states (CMS) were, as follows:

HU/H/320/001, 003 and 004: Austria, Belgium, Germany and Spain,

HU/H/0321/001, 003 and 004: Portugal and Spain,

HU/H/0322/001, 003 and 004: Italy.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Lidorat, Atorvastatin/Amlodipine Richter and Torviman film-coated tablets 10 mg/5 mg, 20 mg/5 mg and 20 mg/10 mg atorvastatin L-lysine/amlodipine besylate. The holder of the marketing authorisation in the RMS is Gedeon Richter Plc.

The marketing authorisation has been granted pursuant to Article 10(b) of Directive 2001/83/EC (fixed combination) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. Bioequivalence of the fixed combination with two monocomponent originator products Sortis® film-coated tablets (containing 10 mg and 20 mg atorvastatin as active ingredient in form of the calcium salt) and Norvasc® tablets (containing 5 mg and 10 mg amlodipine besylate as active ingredient), of Pfizer Inc.

The products are indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease and/or Prinzmetal's angina) in adult patients with one of the following coincident conditions:

- primary hypercholesterolaemia (including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification),
- homozygous familial hypercholesterolaemia,
- need of prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

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 concerning the decentralised application of Atorvastatin/Amlodipin Richter, Lidorat and Torviman 10/5 mg, 20/5 mg and 20/10 mg film-coated tablets is based on Article 10.b of consolidated Directive 2001/83/EC (i.e. a fixed combination). The products have been developed by Gedeon Richter Plc. The rreference products for the bioequivalence study were Sortis film-coated tablets (containing 10 mg and 20 mg atorvastatin as active ingredient in form of the calcium salt) and Norvasc tablets (containing 5 mg and 10 mg amlodipine besylate as active ingredient), original products of Pfizer Inc.

The fixed combination product is indicated as substitution therapy for patients adequately controlled with amlodipine and atorvastatin given concurrently at the same dose level. The indication is treatment of essential hypertension and dyslipidemia consistent with global cardiovascular risk assessment and management recommendations.

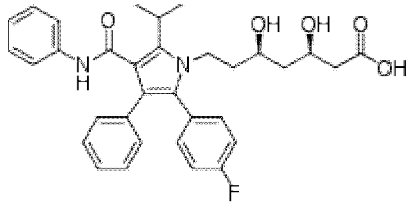
The film-coated tablets will be marketed in dosage strengths of atorvastatin/amlodipine 10/5 mg, 20/5 mg and 20/10 mg packed in PA/Al/PVC//Al blisters and box.

II.2 Drug Substances

II.2.1 Atorvastatin L-lysine

Data on the quality and manufacture of the active substance was provided in the applicant's dossier using the Active Substance Master File (ASMF) procedure. The Quality Overall Summary is adequate.

INN name: atorvastatin
Chemical name: (3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4(phenylcarba-moyl) pyrrol-1-yl]- 3,5-dihydroxyheptanoic acid L-lysine salt
Structure:



$$H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\underset{\displaystyle COOH}{\underset{|}{CH}}\text{-}NH_2$$

The active substance is a white or almost white powder and is slightly soluble in methanol, DMF and water and insoluble in acetone and dichloromethane. It shows polymorphism.

The molecule has two chiral centers, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder supplied complete details of the manufacturing process. Description of the manufacturing process of the API is adequate.

Evidence of the structure has been confirmed by NMR, MS, FT-IR, TG, XRDP, DSC and by UV spectroscopy. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Atorvastatin L-lysine is not official in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: identification by IR and HPLC, water content, sulphated ash, heavy metals, lysine content, related substances, residual solvents, assay and microbiological purity. The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline. 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 active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

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

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

Stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 24 months is acceptable if stored below 30°C in a sealed double polyethylene bags in paper.

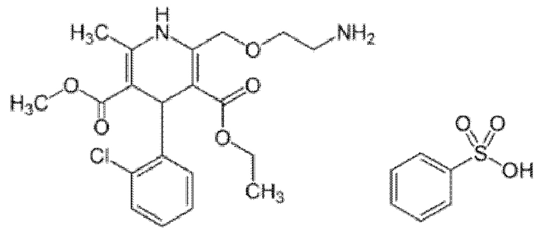
GMP compliance of the API manufacture is demonstrated by the applicant.

II.2.2 Amlodipine besylate

Amlodipine besylate is described in the European Pharmacopoeia (Ph. Eur.) and a Certificate of Suitability of Ph. Eur monograph (CEP) has been granted for this substance. The CEP indicates that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that it is supplemented with a test for residual solvents by GC.

INN name: amlodipine besylate
Chemical name: 3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chloro-phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene-sulphonate

Structure:



The active substance is a white or almost white powder slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

The substance is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents and particle size distribution.

The Ph. Eur. specification includes the following tests for amlodipine besylate: identification (IR), optical rotation, related substances (HPLC), water content, sulphated ash, assay (HPLC). Residual solvents (GC) are also controlled. The specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

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. The in-house analytical methods and the validation of these additional tests have been presented. This is considered to be acceptable.

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 of 5 years and the packaging material (double polyethylene bag in multiple coated paper-bag or fibre drum) have been mentioned on the CEP.

GMP compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the formulation development was to develop a single formulation containing atorvastatin lysine and amlodipine besylate in different dosage strengths.

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 products. 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 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 composition, appearance and packaging was obtained. The excipients used in the finished product are calcium carbonate, microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, calcium oxide, sodium starch glycolate, hydroxypropylcellulose, polysorbate, colloidal anhydrous silica, magnesium stearate and Opadry white (talc, macrogol, titanium dioxide and partially hydrolyzed poly(vinyl alcohol). All excipients used comply with their respective Ph. Eur. monograph with exception of Opadry and calcium oxide, which comply with a satisfactory in-house monograph and USP monograph, respectively. 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.

The 10 mg/5 mg film-coated tablets are white, round, biconvex film-coated tablets, engraving "CE3" on one side.

The 20 mg/5 mg and 20 mg/10 mg film-coated tablets are white, oblong, biconvex film-coated tablets, engraving "CE4" or "CE6" on one side, respectively.

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 study are presented.

The container closure system of the product is as follows: PA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months under storage conditions

"*Store below 25 °C. Store in the original package in order to protect from light and moisture*"

is approved.

The SPC, PIL and label are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

There is nothing against granting of the marketing authorization from chemical-pharmaceutical aspects.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmaco-toxicological properties of both atorvastatin and amlodipine are well-known. The non clinical overview is therefore based on a review of data available in several scientific databases or published in relation to atorvastatin and amlodipine given either alone or in combination.

III.2 Pharmacology

No specific new non-clinical studies have been performed, which is acceptable for this type of application. The application contained a satisfactory literature overview.

Atorvastatin is a selective, competitive inhibitor of HMG‑CoA reductase, the rate-limiting enzyme responsible for the conversion of 3‑hydroxy-3‑methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG‑CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

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

The fix combination product is intended to be used as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination

III.2 Pharmacokinetics

No specific new non-clinical studies have been performed, which is acceptable for this type of application. The application contained a satisfactory literature overview.

Atorvastatin is rapidly absorbed after oral administration. Extent of absorption increases in proportion to atorvastatin dose. Its low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Atorvastatin is mainly bound to plasma proteins.

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Most of the circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation.

After oral administration amlodipine is well absorbed. The bioavailability of Amlodipine is not altered by the presence of food.

The most part of the circulating drug is bound to plasma proteins.

Amlodipine is extensively converted to inactive metabolites via hepatic metabolism, and a smaller part of the parent compound and the majority of the metabolites excreted in the urine. Elimination from the plasma is biphasic.

III.3 Toxicology

No new data but a satisfactory clinical overview have been submitted.

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 folds the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic; however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

In two-year preclinical studies with rats and mice, receiving amlodipine in doses of 0.5 mg, 1.25 mg 2.5 mg per kg body weight, amlodipine was not carcinogen. In mice the highest dose was similar to the advised maximum daily human dose of 10 mg counted in mg/ m^2, while in rats it was the double. This dose was near the maximum tolerated dose in mice, while in rats it was lower.

Amlodipine was not mutagen neither in the study of the chromosomes or gens.

In rats amlodipine did not show any effect on fertility up to 10 mg/kg body weight, which was eight times higher than the maximum human dose counted according to body surface.

III.4 Ecotoxicity/environmental risk assessment

Since Lidorat, Atorvastatin/Amlodipine Richter, Torviman film-coated tablets are intended to substitute other similar products on the market, their storage, distribution, use and disposal will not result in an increase of risk to the environment. No environmental risk assessment is therefore deemed necessary.

III.5 Discussion on the non-clinical aspects

This fix combination product contains atorvastatin lysine salt, in contrast to the marketed atorvastatin products containing atorvastatin calcium salt. Lysine, the natural amino acid being present in foods and human proteins is an acceptable salt-forming substance in human medicines.

The Applicant overviewed the literature with regard to non-clinical data of atorvastatin L-lysine and concluded that it has not been tested in non-clinical studies. As in bioequivalence study, comparing the fix-combination of atorvastatin-amlodipine content with the monocomponent tablets containing amlodipine and atorvastatin, the main pharmacokinetic parameters for atorvastatin L-lysine in the fixed combination and for atorvastatin-calcium in the tested reference preparation were found to be equivalent, no additional studies were needed to be performed to demonstrate the similar non-clinical profile of atorvastatin lysine salt to that of the calcium salt.

Pharmacodynamics, pharmacokinetics and toxicology of both atorvastatin and amlodipine are well-known. As the combination is only for substitution therapy there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The rationale of developing fixed-dose combination products for the concomitant treatment of two concomitant diseases like hypertension and dyslipidaemia is that risk factors for cardiovascular disease often coexist. With the average population prevalence of concomitant hypertension and dyslipidemia estimated at 18% of men and 20% of women, the shortcomings of medical intervention result in an enormous excess burden of morbidity and mortality Guidelines (NCEP 2003, ESC *Guidelines on CVD prevention in clinical practice* 2007) stress this therapeutic approach i.e. the simultaneous management of multiple cardiovascular risk factors.

For the combination product is indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination, the applicant has conducted one bioequivalence study using two well-established monocomponent products of atorvastatin and amlodipine.

IV.2 Pharmacokinetics

IV.2.1 Literature review

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%.

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥98% bound to plasma proteins.

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG‑CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Concentrations of atorvastatin and its active metabolites in women differ from those in men. (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC) These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

After oral administration amlodipine is well absorbed, and peak plasma concentration is achieved between 6-12 hours. Absolute bioavailability has been estimated between 64-80%. The bioavailability of Amlodipine is not altered by the presence of food.

Its distribution volume is about 21 l/kg. Approximately 97 % of the circulating drug is bound to plasma proteins. Steady-state plasma levels of Amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Amlodipine is extensively converted to inactive metabolites via hepatic metabolism, and 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life about 30-50 hours.

V.2.2 Bioequivalence study

In line with the *Question and Answers document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention* (CHMP/EWP/191583/2005) and the revised *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CHMP/EWP/240/95 Rev.1) the applicant has conducted one bioequivalence study entitled "Randomised, open-label, 2-way crossover, bioequivalence study of atorvastatin/amlodipine 20mg-10mg tablet (Gedeon Richter Romania S.A., Romania) and co-administration of Sortis (reference, Pfizer Ltd. Hungary) 20 mg tablet / Norvasc (reference, Pfizer Europe MA EEIG, Romania) 10 mg tablet following a 20 mg-10 mg dose in healthy subjects under fasting conditions".

GCP aspects: the applicant stated that the bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

Study design: the clinical development performed by the applicant comprised of an open-label, single-dose, two-way, crossover study, during which the subjects received a single dose of 20 mg / 10 mg atorvastatin/amlodipine (as fixed combination Atorvastatin/Amlodipine 20 mg / 10 mg film-coated tablets {containing atorvastatin L-lysine and amlodipine besylate}, as 'Treatment A' or co-administered Sortis 20mg film-coated tablets {containing atorvastatin calcium} plus Norvasc 10 mg tablets {containing amlodipine besylate}, as 'Treatment B') in a randomized order. The two treatment phases were separated by an appropriate washout period. For atorvastatin and metabolites as well as for amlodipine, blood samples were collected prior to drug administration and at appropriate intervals.

Altogether 56 volunteers completed the study.

Analytical methods: plasma concentrations of atorvastatin and its active metabolites ortho-hydroxy atorvastatin and para-hydroxy atorvastatin as well as of amlodipine were determined by validated HPLC-MS/MS methods.

The *pharmacokinetic parameters* analysed were AUC0-T, AUC0-inf, Cmax. The bioequivalence assessment is based on pharmacokinetic parameters of atorvastatin and amlodipine. Data of the active metabolites, 2-OH-atorvastatin and 4-OH-atorvastatin are provided but bioequivalence assessment is based on the pharmacokinetic analysis of the parent compounds.

Statistical methods: ANOVA was performed on log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{inf}. To conclude bioequivalence two one sided 90% confidence intervals were calculated for test by reference ratio of geometric least square mean of C_{max}, AUC_{0-t}.

Results

Atorvastatin - Amlodipine (A) vs Sortis - Norvasc (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	96.68%	96.15%	110.34%
90 % Geometric C.I.[2]	92.16 % to 101.41 %	91.78 % to 100.73 %	98.57 % to 123.50 %
Intra-Subject CV	15.21 %	14.78 %	36.81 %

Atorvastatin - Amlodipine (A) vs Sortis - Norvasc (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	102.86%	102.97%	103.99%
90 % Geometric C.I.[2]	99.96 % to 105.84 %	100.04 % to 105.99 %	100.93 % to 107.15 %
Intra-Subject CV	9.04 %	9.15 %	9.48 %

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-inf} Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration

The results of the study showed that the 90% Confidence Intervals for the log-transformed parameters AUC0-t and Cmax for atorvastatin and amlodipine were all within the 80-125% acceptable range.

Based on these results, it can be concluded that the test atorvastatin-amlodipine combination product (Treatment A) is bioequivalent to the individual atorvastatin and amlodipine reference products co administered (Sortis and Norvasc, Treatment B), following a 20 mg-10 mg dose under fasting conditions.

The bioequivalence study was carried out with the highest strength (Atorvastatin-Amlodipine 20/10 mg film-coated tablets) and the applicant requested biowaiver for all other strengths. The applicant stated that all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) concerning biowaivers were met:

- the pharmaceutical products were manufactured by the same manufacturing process;
- atorvastatin and amlodipine did have a linear drug input over the developed dose range;
- dose-proportional formulations;
- in vitro dissolution testing at the required pH values had shown similarity of dissolution profiles.

Thus, the results of bioequivalence study with Atorvastatin/Amlodipine 20 mg / 10 mg formulation can be extrapolated to other strengths: 10mg/5mg and 20mg/5mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

No new data have been submitted. A literature overview describes the main pharmacodynamic characteristics of the active principles. For the combination product is indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination, this is acceptable.

The Lidorat, Atorvastatin/Amlodipine Richter and Torviman products contain atorvastatin lysine salt, in contrast to the marketed atorvastatin products containing atorvastatin calcium salt. Lysine is an acceptable salt-forming substance in human medicines, being a natural amino acid, an essential component of food and one of the building blocks of all human proteins. The mean daily uptake of lysine is about 5.3 g/day {National Academy of Sciences, Institute of Medicine, Food and Nutrition Board, 2005 157 /id}, which far exceeds the maximal lysine exposure using the present products (about 4 mg/day). Therefore, the lysine salt of atorvastatin is considered to be safe unless it alters the pharmacokinetics of atorvastatin. In line with the applicable regulatory guidance documents (i.e. CHMP/EWP/240/95, Rev. 1 and the *Question and Answers document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention* (CHMP/EWP/191583/05)), the applicant's clinical development programme has targeted demonstration of bioequivalence between the new fixed-dose combination product and the free combination of the recognized reference formulations.

For supporting the absence of any clinically significant difference between the present salt alternatives of atorvastatin, the Applicant performed a systematic review of the related scientific literature. As a result of the literature search, up to now, no published study was identified dealing with the clinical investigation of atorvastatin L-lysine. However, publicly available data on the L-lysine itself and the review of general aspects of using alternative salt forming agents, supplemented with human pharmacokinetic data and the results of in vitro tests examining the degree of ionization of both salts in media at bio-relevant pHs led to the conclusion that no other separate clinical study is needed for supporting the proof of similarity of efficacy/safety of the two different atorvastatin salt forms. The applicant compiled a brief summary from literature findings and own laboratory data in order to support the statement above.

As suggested by literature data the following aspects shall be taken into account when changing salt form of an active entity:

- Influence on pharmacokinetics
    - absorption (solubility, dissolution rate),
    - first-pass effect,
    - distribution, metabolism and elimination.
- influence on safety,
- toxicology.

The applicant performed in vitro comparative dissolution tests in media of three different pHs and found that dissolution profiles of test (atorvastatin L-lysine) and reference (atorvastatin calcium) preparations are similar.

In addition, the applicant performed in vitro tests examining the degree of ionization of salts in media at bio-relevant pHs. On the basis of the calculated results, atorvastatin calcium and lysine salts do not differ in ionization degree in the biologically relevant pH range (i.e. gastrointestinal tract's pH). The above results are modelling that practically atorvastatin and calcium as well as L-lysine salts are dissociated completely in the duodeno-jejunal section of the gastrointestinal tract. It is also apparent from the data that the dissociation of both salt forms is complete in the pH range of the blood (pH 7.38-7.42). In other words, atorvastatin molecules are present in the blood circulation in a free (de-protonated) acid form but not as calcium or lysine salt.

As for toxicology, proteins consist of L-amino acids. Lysine cannot be synthesized by mammals and, as a consequence, is an indispensable amino acid. The lysine dose associated with no observed adverse effect level (NOAEL) was estimated at 3.3–4.0 g/kg/day in rats. As a consequence, an upper limit of 300–400 mg/kg/day can be considered in humans. L-Lysine is an acceptable salt-forming substance and flavouring agent in human medicines, being a natural amino acid, an essential component of food and one of the building blocks of all human proteins. Joint WHO/FAO/UNU Expert Consultation attributed “No safety concern” to the use of L-lysine as a flavouring agent. The Consultation has not evaluated L-lysine using the Procedure for the Safety Evaluation of Flavouring Agents, since the substance is a macronutrient and normal component of protein and, as such, human exposure through food is orders of magnitude higher than the anticipated level of exposure from use as flavouring agent. The same conclusion can be reached when considering the ratio between the above mentioned intake in the Western human diet and the maximal lysine exposure using the applicant's product (5.24mg/day): it is around 5.0 o/ooo for a person 70 kg in weight.

Of the nitrogen bases, the essential basic amino acids (e.g. L-lysine) are of no concern.

Based on kinetic considerations, agents of high solubility, dissolution rate and absorption rate may cause unwanted or toxic effects earlier or more strongly expressed when compared to less soluble, hence slow-dissolving, and, in consequence, slow-absorbed salts. The toxicological profile of an active ingredient may, therefore, vary with the selected salt form and provide opportunities to modulate the pharmacodynamic as well as toxic effects. Conversely, when drug salts with similar solubility and dissolution rates are compared, the same safety profiles may be expected provided the typical difference in the time course of plasma concentrations resulting from different absorption rates for identical doses of a drug entity, but the same value of the elimination rate constant.

IV.4 Clinical efficacy

The applicant's supportive efficacy analysis was restricted to randomized and controlled studies in the treatment of concomitant hypertension and dyslipidaemia. These studies showed the lack of negative pharmacodynamic interaction between the two drugs: the lipid lowering efficacy of atorvastatin was preserved when concomitant amlodipine therapy was added, and the blood pressure lowering efficacy of amlodipine was preserved when concomitant atorvastatin therapy was added to the patients.

The rationale of developing a fixed combination product of atorvastatin and amlodipine was further supported by extensive co-prescription data of amlodipine and atorvastatin in the clinical practice, obtained from a reliable source.

The applicant has not performed dose-finding studies. However, the published studies identified in the literature could help the applicant's dose selection, since some studies reported the relative proportions of the different dose pairs after a free individual dose titration period. The percentage of patients receiving the 5mg/10mg, 5mg/20mg, and 10mg/20mg dose pairs after the individual dose titration period in the GEMINI study were 17.8%, 19.5%, 13.0%, and 12.5%, respectively (all together, 62.8%). In the AVALON study (part 3), at the end of the free dose titration period, similar number of patients were treated with 5 mg or 10 mg of amlodipine (50.2% and 49.8%) while with respect to atorvastatin, the majority of patients were treated with 10 mg (32.1%) or 20 mg (32.0%), and only 23.2% received 40 mg and 12.7% received 80 mg.

For further justification the applicant has provided co-prescription data from four European Union member states. These data support the widespread and generally increasing concomitant use of atorvastatin and amlodipine.

IV.5 Clinical safety

The safety of atorvastatin and amlodipine as monocomponents has already been demonstrated during the clinical development of both substances.

As for the atorvastatin/amlodipine combination, the applicant's supportive safety analysis dealt with all available published data on the combined use of these active pharmaceutical ingredients. In brief, the supportive safety analysis of the published data (on more than 10,000 exposed patients) found that the discontinuation rates were similar between arms in the comparative studies, and the reported adverse event frequencies with the combination were similar to those in the comparator arms (monotherapy or placebo) or to the reported frequencies of the approved monotherapy products according to their approved Summary of Product Characteristics.

IV.6 Discussion on the clinical aspects

The application concerns a fixed combination of atorvastatin and amlodipine. The indication is as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease) in adult patients with one of the following coincident conditions:

- primary hypercholesterolaemia (including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification),
- homozygous familial hypercholesterolaemia,
- need of prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

The non-significance of the salt-forming agents of atorvastatin (lysine in this application and calcium in the reference product) has been supported appropriately.

To support the submission the applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time.

For justification, the applicant provided both literature and co-prescription data, the latter from four EU member states. The co-prescription data support the widespread and generally increasing concomitant use of atorvastatin and amlodipine.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for these combination products contains an adequate review of published non-clinical, clinical and co-prescription data as well as the bioequivalence with established reference products of the monocomponents atorvastatin and amlodipine (Sortis® film-coated tablets and Norvasc® tablets, respectively) of Pfizer Inc. The quality of the products is adequately drawn up to support the consistent safety and efficacy of the combination film-coated tablets. Approval was recommended by the RMS and agreed by the CMSs.

The bioequivalence study has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD*h*. Agreement between member states was reached during the written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for these combination products and the original mono-component reference ones, and have therefore granted the marketing authorisation.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The Reference Member State considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected occurring either in the Community or in a third country.

V.1.3 Risk Management Plan

The applicant adequately identified the safety concerns possibly connected with the use of these combination products and gave assurance that its routine pharmacovigilance activities as well as information and warnings given by the Summary of Product Characteristics and the Patient Leaflet give acceptable assurance to their minimisation.

V.1.4 Periodic Safety Update Report (PSUR)

The applicant proposed to use the European Harmonised Birthday of atorvastatin and amlodipine as published by the Head of Agencies and go straight into a PSUR cycle of 3 years with identification of the first Data Lock Point. This is acceptable.

V.1.5 Legal status

Prescription-only medicine

V.2 Summary of Product Characteristics (SmPC)

The SmPC is in the agreed template and is, both from pharmaceutical and biomedical points of view acceptable.

V.3. Package Leaflet and user consultation

The package leaflet and labelling are in the agreed templates.

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

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

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

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