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Public Assessment Report

Name of the Product:

Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets

(ezetimibe/atorvastatin)

Procedure number: HU/H/0701/001-004/DC

Marketing authorisation holder: Qualipharmacon Kft.

Date: 25. 01. 2022.

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets. The holder of the marketing authorisation is Qualipharmacon Kft.

The active substances are ezetimibe and atorvastatin.

- Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg film-coated tablets: each film-coated tablet contains 10 mg of ezetimibe and 10 mg of atorvastatin (as calcium trihydrate).
- Ezetimibe/Atorvastatin Qualipharmacon 10 mg/20 mg film-coated tablets: each film-coated tablet contains 10 mg of ezetimibe and 20 mg of atorvastatin (as calcium trihydrate).
- Ezetimibe/Atorvastatin Qualipharmacon 10 mg/40 mg film-coated tablets: each film-coated tablet contains 10 mg of ezetimibe and 40 mg of atorvastatin (as calcium trihydrate).
- Ezetimibe/Atorvastatin Qualipharmacon 10 mg/80 mg film-coated tablets: Each film-coated tablet contains 10 mg of ezetimibe and 80 mg of atorvastatin (as calcium trihydrate).

The other ingredients are:

- tablet core: cellulose microcrystalline 101; mannitol; calcium carbonate; croscarmellose sodium; hydroxypropylcellulose, polysorbate 80, iron oxide, yellow (E172); magnesium stearate; povidone K29/32; sodium laurilsulfate.
- tablet coat:
    - Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg film-coated tablets - Opadry White OY-L28900 consisting of: lactose monohydrate; hypromellose 2910 (E464); titanium dioxide (E171); macrogol 4000 (E1521).
    - Ezetimibe/Atorvastatin Qualipharmacon 10 mg/80 mg film-coated tablets - DrCoat FCU consisting of: hypromellose 2910; titanium dioxide (E171); talc (E553b); macrogol 400; iron oxide yellow (E172).

The appearance of the tablets is:

- The 10 mg/10 mg film-coated tablets are white, round, biconvex film-coated tablets., with diameter 8.1 mm approximately.
- The 10 mg/20 mg film-coated tablets are white, ovaloid, biconvex film-coated tablets., with dimensions 11.6 × 7.1 mm approximately.
- The 10 mg/40 mg film-coated tablets are white, capsule shape, biconvex film-coated tablets., with dimensions 16.1 × 6.1 mm approximately.
- The 10 mg/80 mg film-coated tablets are yellow, oblong, biconvex film-coated tablets., with dimensions 19.1 × 7.6 mm approximately.

The tablets are available in packs in blisters.

Ezetimibe/Atorvastatin Qualipharmacon is a medicine to lower increased levels of cholesterol. Ezetimibe/Atorvastatin Qualipharmacon contains ezetimibe and atorvastatin.

Ezetimibe/Atorvastatin Qualipharmacon is used in adults to lower levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, Ezetimibe/Atorvastatin Qualipharmacon raises levels of "good" cholesterol (HDL cholesterol).

Ezetimibe/Atorvastatin Qualipharmacon works to reduce the cholesterol in two ways. It reduces the cholesterol absorbed in the digestive tract, as well as the cholesterol the body makes by itself.

Cholesterol is one of several fatty substances found in the bloodstream. The total cholesterol is made up mainly of LDL and HDL cholesterol.

LDL cholesterol is often called "bad" cholesterol because it can build up in the walls of the arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke.

HDL cholesterol is often called "good" cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease.

Triglycerides are another form of fat in the blood that may increase the risk for heart disease.

The doctor may prescribe Ezetimibe/Atorvastatin Qualipharmacon if patients are already taking both atorvastatin and ezetimibe at the same dose level, as substitution therapy, in addition to their cholesterol lowering diet if they have:

- a raised cholesterol level in the blood (primary heterozygous familial and non-familial hypercholesterolaemia) or elevated fat levels in the blood (mixed hyperlipidaemia)

- a hereditary illness (homozygous familial hypercholesterolaemia) that increases the cholesterol level in the blood

Ezetimibe/Atorvastatin Qualipharmacon does not help patients lose weight.

What patients need to know before using Ezetimibe/Atorvastatin Qualipharmacon

Patients must not take Ezetimibe/Atorvastatin Qualipharmacon if they
- are allergic to atorvastatin, ezetimibe or any of the other ingredients of this medicine;
- have or have ever had a disease that affects the liver;
- have had any unexplained abnormal blood tests for liver function;
- are a woman able to have children and are not using reliable contraception;

- are pregnant, trying to become pregnant or are breast-feeding;
- use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C.

Warnings and precautions

Before taking Ezetimibe/Atorvastatin Qualipharmacon, the doctor or pharmacist should be contacted if patients

- have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes;
- have kidney problems;
- have an under-active thyroid gland (hypothyroidism);
- have had repeated or unexplained muscle aches or pains, a personal history of family history of muscle problems;
- have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other "statin" or fibrate" medicines);
- are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and Atorvastatin/Ezetimibe containing medicines can lead to serious muscle problems (rhabdomyolysis);
- regularly drink a large amount of alcohol;
- have a history of liver disease;
- are older than 70 years.

If patients experience unexplained muscle pain, tenderness, or weakness while taking Ezetimibe/Atorvastatin Qualipharmacon, the doctor should be contacted promptly.This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. Atorvastatin is known to cause muscle problems, and cases of muscle problems have also been reported with ezetimibe.

If patients have a muscle weakness that is constant, the doctor or pharmacist should be told. Additional tests and medicines may be needed to diagnose and treat this.

Before taking Ezetimibe/Atorvastatin Qualipharmacon the doctor or pharmacist should be checked with

- if patients have severe respiratory failure.

If any of these apply to patients (or they are not sure), before taking Ezetimibe/Atorvastatin Qualipharmacon the doctor or pharmacist should be talked to, because the doctor will need to carry out a blood test before and possible during the treatment to predict the risk of muscle-related side effects. The risk of muscle-related side effects, e.g. rhabdomyolysis (breakdown of damaged skeletal muscle), is known to increase when certain medicines are taken at the same time.

While patients are on this medicine the doctor will monitor them closely if they have diabetes or are at risk of developing diabetes. They are likely to be at risk of developing diabetes if they have high levels of sugars and fats in their blood, are overweight and have high blood pressure.

The doctor should be told about all medical conditions including allergies.

Children and adolescents

Ezetimibe/Atorvastatin Qualipharmacon is not recommended for children and adolescents.

Other medicines and Ezetimibe/Atorvastatin Qualipharmacon

The doctor or pharmacist should be told if patients are taking, have recently taken any other medicines or might take any other medicines.

Fibrates (medicines for lowering cholesterol) should be avoided while taking Ezetimibe/Atorvastatin Qualipharmacon.

There are some medicines that may change the effect of Ezetimibe/Atorvastatin Qualipharmacon or the effect of other medicines may be changed by Ezetimibe/Atorvastatin Qualipharmacon. 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":

- ciclosporin (a medicine often used in organ transplant patients);
- erythromycin, clarithromycin, telithromycin, fusidic acid, rifampicin (medicines for bacterial infections);
- ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole (medicines for fungal infections);
- gemfibrozil, other fibrates, nicotinic acid, derivatives, colestipol, colestyramine (medicines for regulating lipid levels);
- some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, diltiazem;
- digoxin, verapamil, amiodarone (medicines to regulate the heart rhythm);
- letermovir, a medicine that helps stop patients from getting ill from cytomegalovirus;
- medicines used in the treatment of HIV, e.g., ritonavir, lopinavir, atazanavir, indinavir, darunavir, the combination of tipranavir/ritonavir, etc. (medicines for AIDS);
- some medicines used in the treatment of hepatitis C, e.g., telaprevir, boceprevir and the combination of elbasvir, grazoprevir;
- daptomycin (a medicine used to treat complicated skin and skin structure infections and bacteraemia);
- if patients need to take oral fusidic acid to treat a bacterial infection they will need to temporarily stop using this medicine. The doctor will tell them when it is safe to restart Ezetimibe/Atorvastatin Qualipharmacon. Taking Ezetimibe/Atorvastatin Qualipharmacon with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis).

- Other medicines known to interact with the combination product
    - oral contraceptives (medicines for preventing pregnancy);
    - stiripentol (an anticonvulsant medicine for epilepsy);
    - cimetidine (a medicine used for heartburn and peptic ulcers);
    - phenazone (a painkiller);
    - antacids (indigestion products containing aluminium or magnesium);

- warfarin, phenrprocoumon, acenocoumarol or fluindione (medicines to prevent blood clots);
- colchicine (used to treat gout);
- St John´s Wort (a medicine to treat depression).

Ezetimibe/Atorvastatin Qualipharmacon with food and alcohol

Grapefruit juice
More than one or two small glasses of grapefruit juice should not be taken per day because large quantities of grapefruit juice can change the effects of the combination product.

Alcohol
Drinking too much alcohol should be avoided while taking this medicine.

Pregnancy and breast-feeding and fertility

Ezetimibe/Atorvastatin Qualipharmacon cannot be taken if patients are pregnant, are trying to become pregnant or think they may be pregnant.

Ezetimibe/Atorvastatin Qualipharmacon cannot be taken if patients are able to become pregnant unless they use reliable contraceptive measures. If they get pregnant while taking Ezetimibe/Atorvastatin Qualipharmacon, taking it should be stopped immediately and the doctor should be told.

Ezetimibe/Atorvastatin Qualipharmacon cannot be taken if patients are breast-feeding.

If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, the doctor or pharmacist should be asked for advice before taking this medicine.

Driving and using machines

Ezetimibe/Atorvastatin Qualipharmacon is not expected to interfere with the ability to drive or to use machinery. However, it should be taken into account that some people may get dizzy after taking Ezetimibe/Atorvastatin Qualipharmacon. If patients feel dizzy after taking this medicine driving and using machines are not allowed.

Ezetimibe/Atorvastatin Qualipharmacon contains lactose

If patients have been told by the doctor that they have an intolerance to some sugars, before taking this medicinal product the doctor should be contacted.

Ezetimibe/Atorvastatin Qualipharmacon contains sodium

Ezetimibe/Atorvastatin Qualipharmacon contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ´sodium-free

How to use Ezetimibe/Atorvastatin Qualipharmacon

This medicine must always be taken exactly as the doctor or pharmacist has told. The doctor will determine the appropriate tablet strength for patients, depending on their current treatment and their personal risk status. If patients are not sure the doctor or pharmacist should be checked with.

- Before starting Ezetimibe/Atorvastatin Qualipharmacon, patients should be on a diet to lower their cholesterol.
- Patients should stay on this cholesterol-lowering diet while taking Ezetimibe/Atorvastatin Qualipharmacon.

How much to take
The recommended dose is one Ezetimibe/Atorvastatin Qualipharmacon tablet once a day preferably always at the same time. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water).

When to take
Ezetimibe/Atorvastatin Qualipharmacon can be taken at any time of the day. It can be taken with or without food.

If the doctor has prescribed Ezetimibe/Atorvastatin Qualipharmacon along with colestyramine or any other bile acid sequestrant (medicines for lowering cholesterol), Ezetimibe/Atorvastatin Qualipharmacon should be taken at least 2 hours before or 4 hours after taking the bile acid sequestrant.

What to do if more Ezetimibe/Atorvastatin Qualipharmacon was taken that it should have been?

In the event of taking more tablets than it is advised, the doctor or pharmacist should be contacted.

What to do if taking Ezetimibe/Atorvastatin Qualipharmacon was forgotten?

No double dose to make up for a forgotten dose can be taken. Patients should take their normal dose at the usual time the next day.

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

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If patients experience any of the following serious side effects or symptoms, taking the tablets should be stopped and the doctor should be told immediately or they should go to the nearest hospital accident and emergency department and their tablets should be taken with them.

- 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, pain, rupture or red-brown discolouration of urine and particularly, if at the same time, patients feel unwell or have a high temperature if may be caused by an abnormal muscle breakdown which can be life-threatening and lead to kidney problems;
- lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

Patients should consult the doctor as soon as possible if they experience problems with unexpected or unusual bleeding or bruising, because this may be suggestive of a liver complaint.

Other possible side effects with Ezetimibe/Atorvastatin Qualipharmacon:

Common: (may effect up to 1 in 10 people)
- inflammation of the nasal passage, pain in the throat, nose bleed;
- allergic reactions;
- increasing blood glucose level, diabetic patients should monitor their blood glucose level;
- headache;
- nausea, constipation, flatulence, diarrhoea, indigestion, abdominal pain;
- pain in the pharynx and/or larynx;
- pain of the joints and/or hands or feet, back pain, muscle pain (myalgia), muscle spasm, joint swelling;
- elevations in some laboratory blood tests of muscle function (creatin kinase (CK);
- abnormal liver function test results, elevations in some laboratory blood tests of liver function (transaminases);
- feeling tired.

Uncommon: (may affect up to 1 in 100 people)
- swellings due to an allergic reaction;
- reduced blood glucose level, diabetic patients should monitor their blood glucose level;
- loss of appetite, weight gain;
- cough;
- muscle weakness, neck pain, chest pain;
- hot flashes, high blood pressure, slower heart beat;
- vomiting, belching, inflammation of the pancreas and the liver, heartburn, inflammation of the stomach membranes, dry mouth, bloating;
- redness of the skin, hives, skin rash, itching, hair loss;
- nightmares, difficulty sleeping;
- dizziness, numbness, impaired sense of taste, amnesia, local abnormal sensations;
- blurred vision;
- ringing in the ears;
- feeling of general discomfort, uneasiness or pain;
- weakness;
- increased liver enzyme gamma-glutamyltransferase;
- positive urine test on white blood cells.

Rare: (may effect up to 1 in 1000 people)
- reduction of blood platelets;

- swelling of the lower layer of skin tissue of the face, tongue, throat, abdomen, arms or legs (angioneurotic oedema);
- widespread rash forming sharply demarcated red patches or rash with blisters and pealing skin, particularly around the mouth, nose, eyes and genitals due to an allergic reaction;
- inflammation of the skeletal muscle, inflammation of the tendon sometimes complicated by rupture, muscle weakness due to a loss of skeletal muscle fibers;
- visual disturbances;
- yellowing of the skin and of the whites of the eyes.

Very rare: (may effect up to 1 in 10000 people)
- anaphylactic shock by allergic reaction;
- hearing loss;
- liver failure;
- increase of the size of male breasts.

Unknown frequency (that cannot be estimated from the available data) are
- allergic reaction including rash and swelling of the lower layers of the skin;
- shortness of breath, inflammation of the gall bladder, gallstones;
- physical weakness and loss of strength, loss of muscle tissue by auto-immune antibodies;
- depression.

Additionally, the following side effects have been reported during post-marketing for some statins (medicines used to lower cholesterol):
- breathing problems including persistent cough and/or shortness of breath or fever;
- diabetes: this is more likely if patients have high levels of sugars and fats in their blood, are overweight and have high blood pressure;
- sexual difficulties.

How to store Ezetimibe/Atorvastatin Qualipharmacon

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

This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets. The procedure was finalised at 14 September 2021. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

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

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Spain, Poland) concerned ezetimibe/atorvastatin 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets.

The application has been filed pursuant to Article 8(3) of Directive 2001/83/EC ("full-mixed" application).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets from Qualipharmacon Kft.

The product is indicated for the following:
as an adjunct to diet is indicated as substitution therapy for treatment of adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia already controlled with atorvastatin and ezetimibe given concurrently at the same dose level as in the fixed dose combination product, but as separate products.

and also
for the adjuvant as substitution therapy of adults with homozygous familial hypercholesterolemia (HoFH) when given with diet. Patients may also receive other adjunctive treatment (e.g. low density lipoprotein (LDL) apheresis).

Both active substances are well-known with established clinical use.
Atorvastatin, an HMG-CoA reductase inhibitor, was initially launched in EU on 7th November, 1996. (Sortis, Lipitor, Pfizer Limited). Atorvastatin is indicated as an adjunct to diet for the treatment of hypercholesterolemia and prevention of cardiovascular disease.
Ezetimibe, a cholesterol absorption inhibitor, was initially launched on 17th October 2002 in EU (Ezetrol, MSD) for the treatment of hypercholesterolemia. Ezetimibe co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary hypercholesterolaemia who are not appropriately controlled with a statin alone.
Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.
Ezetimibe is also indicated for the prevention of cardiovascular events.

To support the application, the applicant has submitted as report one bioequivalence study.

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

II. QUALITY ASPECTS

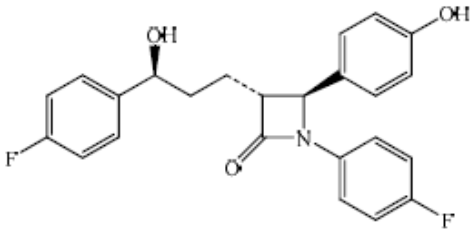
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets via a decentralized procedure according to Article Article 8 (3) of consolidated Directive 2001/83/EC (i.e. dossier with administrative, quality, pre-clinical and clinical data). The reference products are Lipitor 80 mg film-coated tablets (containing 80.0 mg atorvastatin as active ingredient), and Ezetrol® 10 mg tablets (containing 10 mg ezetimibe as active ingredient) manufactured by Pfizer GmbH and by Schering-Plough Labo (MSD), respectively.

II.2 Drug substance - Ezetimibe

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Ezetimibe
Chemical name: (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxy-propyl]-4-(4-hydroxyphenyl)-2-azetidinone
Structure:



The active substance is white to an off-white crystalline powder, freely soluble in methanol and acetone, soluble in ethanol; practically insoluble in water. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by a suitable battery of well-established spectroscopic methods and specific optical rotation. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Ezetimibe is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, solubility, identification, water content, heavy metals, specific optical rotation, residue on ignition, related substances, isomer testing, assay, residual solvents and particle size distribution. The presented specification is in accordance with the Ph.Eur. general monograph on Substances for Pharmaceutical Use and the ICH Q6A guideline.

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.

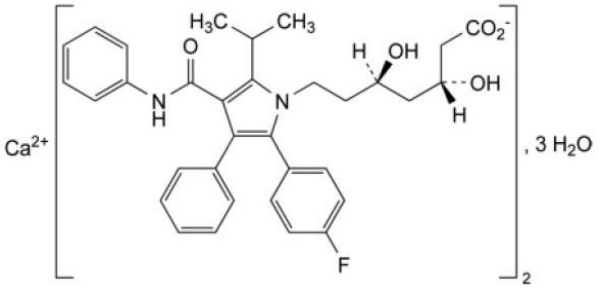
Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable when the API is preserved in well-closed containers at controlled room temperature i.e., 20°C and 25°C.

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

II.3 Drug Substance - Atorvastatin calcium trihydrate

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: Atorvastatin calcium trihydrate
Chemical name: Calcium (3R,5R)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenyl carbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate trihydrate
Structure:



The active substance is white to off-white powder, very slightly soluble in water, slightly soluble in ethanol (96%), practically insoluble in methylene chloride. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph.Eur. monograph, additional specification has only been set for residual solvents, residual catalyst and particle size distribution.
The Ph. Eur. specification includes the following tests for Atorvastatin calcium trihydrate: appearance, solubility, identification, enantiomeric purity, related substances, sodium, water and assay.

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

The retest period and the packaging material (double polyethylene bag in a triple laminated bag placed in container) have been mentioned on the CEPs.

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

II.4 Medicinal product

The aim was to develop film-coated tablets containing ezetimibe and atorvastatin as drug substances in 10 mg or 10/20/40/80 mg doses; bioequivalent and pharmaceutically equivalent to the reference medicinal products Ezetrol tablets and Lipitor film-coated tablets, the branded original products of Schering-Plough Labo (MSD) and Pfizer GmbH, respectively.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.
10 mg/ 10 mg film-coated tablets: White, round, biconvex film-coated tablets.
10 mg/ 20 mg film-coated tablets: White, ovaloid, biconvex film-coated tablets.
10 mg/ 40 mg film-coated tablets: White, capsule shape, biconvex film-coated tablets.
10 mg/ 80 mg film-coated tablets: Yellow, oblong, biconvex film-coated tablets.

The excipients used in the tablet core of finished product are microcrystalline cellulose (type 101), mannitol, calcium carbonate, croscarmellose sodium, hydroxypropylcellulose, polysorbate 80, yellow iron oxide (E172), magnesium stearate, povidone K29/32 and sodium laurilsulfate. As coating agent, Opadry White OY-L28900 is used in case of 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg strengths, which is consist of lactose monohydrate, hypromellose 2910, titanium dioxide (E171) and macrogol 4000. For 10 mg/80 mg strength, DrCoat FCU is used as a film-coating, consisting hypromellose 2910, titanium dioxide (E171), talc, macrogol 400 and yellow iron oxide (E172). All excipients used in the tablet core comply with their respective European Pharmacopoeia monograph. An appropriate in-house specification has been set for film-coating agents. 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 study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister or perforated unit-dose 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. 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.

II.5 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substances are well known. The applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology studies have been presented and no such studies have been required.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant and no such studies were required.

III.4 Toxicology

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

III.5 Ecotoxicity/environmental risk assessment (ERA)

Atorvastatin/Ezetimibe fixed dose combination drug product is meant for substitution indication; therefore this combination is indicated for those patients who have already been treated with the same doses of both medicinal drug products. Placing on the market of this fixed dose combination drug product will not increase the volume of sold atorvastatin or ezetimibe containing products.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of the active substances are well-known. No new non-clinical studies are needed. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamics, pharmacokinetics, efficacy and safety of the active substances are well established.

To support the application, the applicant has submitted as report one bioequivalence study.

IV.2 Pharmacokinetics

Absorption

Atorvastatin
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. 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%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Ezetimibe
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as 10-mg tablets.

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

Ezetimibe
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Biotransformation
Atorvastatin
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.

Ezetimibe
Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination
Atorvastatin
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product 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.
Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Ezetimibe
Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Clinical study report

Pharmacokinetic interaction
The application has detailed the information on the potential pharmacokinetic interaction of atorvastatin and ezetimibe, which indicated that clinically significant pharmacokinetic interaction is not likely. Although increased level (Cmax) of ezetimibe could be observed when taken concomitantly with atorvastatin, this difference is deemed negligible.

Pharmacokinetic study
In order to demonstrate pharmacokinetics of the fixed-dose combination, 1 pivotal bioequivalence study was conducted under fasting conditions with the highest strength of Atorvastatin/Ezetimibe 80mg/10 mg tablets compared to the concomitantly given Lipitor 80 mg film-coated tablets and Ezetrol® 10 mg tablets.
The conduct of the study was satisfactory and the results comply with the acceptance criteria for bioequivalence as detailed in the relevant CHMP guideline.

Study design

The study was a comparative, open-label, randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 80 healthy male and female volunteers under fasting conditions, with 11-days of wash out period.

The objective of this study was to evaluate the comparative bioavailability between Ezetimibe/Atorvastatin 10mg/ 80 mg film-coated tablets (Elpen – Test) and the combination of References: Lipitor® 80 mg film-coated tablets (Pfizer, Germany) and Ezetrol 10 mg Tablets (Schering-Plough Labo N-V., Belgium) after a single-dose in healthy subjects.

In each period, 27 blood samples were obtained. Blood samples were collected prior to study drug administration and 0.17, 0.25, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after the drug administrations in each period.

Bioanalytics

A validated LC-ESI-MS/MS bioanalytical method developed for the quantification of Ezetimibe, Ezetimibe Phenoxy Glucuronide, Atorvastatin and its metabolite 2-Hydroxy Atorvastatin & 4-Hydroxy Atorvastatin in plasma was employed for subjects sample analysis.

Statistical methods

Pharmacokinetics: parametric ANOVA was applied to log-transformed AUC0-t, Cmax, AUC0-inf, and untransformed λ and T1/2, geometric confidence intervals were calculated for AUC0-t, AUC0-inf and Cmax.

Bioequivalence criteria:

Acceptance range for bioequivalence was 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio (T/R) of Cmax and AUC0-t for atorvastatin and ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe (conjugated)).

Summary results:

Atorvastatin:

Parameters (Units)	Geometric Least Squares Means and it's ratio (N = 75)			ISCV %	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	81.320	84.763	95.94	37.32	86.96 % - 105.84 %	98.12
AUC_{0-t} (hr*ng/mL)	317.912	316.256	100.52	19.55	95.36 % - 105.96 %	100.00

Unconjugated ezetimibe:

Parameters (Units)	Geometric Least Squares Means and it's ratio (N = 75)			ISCV %	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	10.047	12.741	78.86	28.08	73.16 % - 84.99 %	99.92
AUC_{0-t} (hr*ng/mL)	89.198	97.776	91.23	17.33	87.06 % - 95.60 %	100.00

Total ezetimibe:

Parameters (Units)	Geometric Least Squares Means and it's ratio (N = 75)			ISCV %	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	125.621	137.668	91.25	17.81	86.97 % - 95.74 %	100.00
AUC_{0-t} (hr*ng/mL)	876.017	932.089	93.98	14.55	90.35 % - 97.76 %	100.00

The 90% confidence intervals of the ratios of LSM derived from analyses on the ln-transformed PK parameters of AUC0-t and Cmax for unconjugated ezetimibe in plasma were not within the predefined protocol limits, nevertheless the acceptance criteria (80.00% to 125.00%) were met for atorvastatin and total ezetimibe respectively, indicating bioequivalence with the Reference products. "*Because of extensive hepatic recirculation, the exposure of ezetimibe is less representative to evaluate the rate of absorption than the metabolite. In this particular case, total (parent + glucuronide metabolite) should be used as analyte for bioequivalence evaluation." (EMA/CHMP/802491/2018, Ezetimibe tablet 10 mg product-specific bioequivalence guidance*)

Conclusion of the bioequivalence study

The results of the bioequivalence study comply with the requirements of the (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) Guideline on the Investigation of Bioequivalence. Therefore essential similarity for the Applicant's combination product of atorvastatin+ezetimibe and the originator Lipitor® 80 mg film-coated tablets (Pfizer) and Ezetrol® 10 mg tablets (Schering-Plough Labo N-V.) has been established.

Biowaiver

In accordance with the Guideline on the Investigation of Bioequivalence the pivotal study performed on the highest strength combination of Atorvastatin/Ezetimibe 80mg/10 mg has been used to waive bioequivalence studies for the lower strengths: 40mg/10mg, 20mg/10mg and 10mg/10mg. The tablets are consisting of two layers (bilayer tablets) so each active ingredient is tableted in a separate layer of the tablet.

- Atorvastatin shows linear pharmacokinetics in the claimed dose range, while ezetimibe is used in the same amount.
- All strengths were manufactured by the same manufacturing process.
- Qualitative composition of the different strengths is the same.
- The composition of the different strengths is quantitatively proportional.
- The dissolution profiles for the 10mg/10mg, 20mg/10mg and 40mg/10mg strengths are similar to the 80mg/10mg strength.

As pharmacokinetics of atorvastatin is linear (and the amount of ezetrol is the same) and all the stipulated biowaiver criteria are fulfilled (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) additional in vivo studies for the bioequivalence assessment of the 10 mg/ 10 mg, 20 mg/ 10 mg and 40 mg/ 10 mg Atorvastatin/Ezetimibe combination may be waived.

IV.3 Pharmacodynamics

Ezetimibe/Atorvastatin Qualipharmacon contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. It reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol absorption and synthesis.

Atorvastatin
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.

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.

Ezetimibe
Ezetimibe inhibits the intestinal absorption of cholesterol. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction.

IV.4 Clinical efficacy

Atorvastatin and ezetimibe are well-known active substances with established efficacy and tolerability profiles. In accordance with EMA guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr** (Guideline on the Investigation of Bioequivalence) and EMA guideline EMA/CHMP/158268/2017 (Guideline on clinical development of fixed combination medicinal products) no dedicated clinical efficacy and safety studies have been performed with the proposed drug product. Therefore, clinical evaluation of the fixed dose combination of atorvastatin/ezetimibe film-coated tablets is based on the presented literature data relevant to each active substance and references to the combinations of statins and ezetimibe published in scientific literature with the aim of proving the clinical benefit provided by the combination.

Specific studies with published results have been identified in the literature that investigated the clinical efficacy of co-administered atorvastatin and ezetimibe, which all proved the superiority of co-administered atorvastatin and ezetimibe over comparators in LDL-C lowering.

Additionally, further clinical trials evaluating the safety and efficacy of concomitant use of ezetimibe with a statin other than atorvastatin have been included in the clinical overview.

Data of the use of the combination in France, Greece, Spain, Italy, Germany and in Hungary has also been provided.

IV.5 Clinical safety

The individual components (atorvastatin and ezetimibe) comprising the proposed drug product have well-established clinical use and well-characterized safety and efficacy profiles. Clinical safety and efficacy of atorvastatin and ezetimibe have been studied in well-controlled randomized clinical studies.
The present application is based on a full, but mixed dossier comprising data from literature as well as the demonstration of bioequivalence of the proposed drug product with the reference products. This study included the evaluation of safety parameters as well.
Safety data of patients treated with the combination have also been provided based on literature data.

Overall, the combined safety data from these different sources provide an acceptable overview of the safety of the FDC of atorvastatin and ezetimibe.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The MAH 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.

IV.6.2 Risk Management Plan

(Version number: 0.2 Date of final sign off: 14/04/2021)

Summary of safety concerns

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

Taking into account of the well-known safety profile of the components and that the indication is only substitution therapy, routine pharmacovigilance activity is sufficient to further characterise the risks of the combination products containing ezetimibe and atorvastatin. There is no need for additional risk minimisation measures to prevent or mitigate the risks, specific clinical activities are known and acted upon by physicians.

Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient by the MAH to manage all of the safety concerns connected to Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets.

No additional activities are proposed.

Risk Minimisation Measures

Qualipharmacon has stated 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 Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets.

IV.6.3 Periodic Safety Update Reports

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.7 Discussion on the clinical aspects

The applications concern a full-mixed application under Article 8(3) of Directive 2001/83/EC as amended.

The product is indicated for the following:
as an adjunct to diet is indicated as substitution therapy for treatment of adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia already controlled with atorvastatin and ezetimibe given concurrently at the same dose level as in the fixed dose combination product, but as separate products.

and also
for the adjuvant as substitution therapy of adults with homozygous familial hypercholesterolemia (HoFH) when given with diet. Patients may also receive other adjunctive treatment (e.g. low density lipoprotein (LDL) apheresis).

To support the application, the Applicant has submitted as report one bioequivalence study.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets. The applicant and the future holder of authorisation is Qualipharmacon Kft.

The application was submitted according to Article 8(3) of Directive 2001/83/EC ("full-mixed" application).

The product is indicated for the following:
as an adjunct to diet is indicated as substitution therapy for treatment of adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia already controlled with atorvastatin and ezetimibe given concurrently at the same dose level as in the fixed dose combination product, but as separate products.

and also
for the adjuvant as substitution therapy of adults with homozygous familial hypercholesterolemia (HoFH) when given with diet. Patients may also receive other adjunctive treatment (e.g. low density lipoprotein (LDL) apheresis).

To support the application, the Applicant has submitted as report one bioequivalence study.

The application contains an adequate review of published clinical data.
The active substances ezetimibe and atorvastatin have well known medicinal use with recognized efficacy and an acceptable level of safety in clinical medicine as outlined in the Clinical Overview. The compound is both effective and safe when used in accordance with recommendations published in the literature.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Ezetimibe/Atorvastatin Qualipharmacon 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets from Qualipharmacon Kft.

V.2 Classification

Prescription only

V.3 Package Leaflet and user consultation

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

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

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

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

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
A.2. b) for Nationally Authorised Products - Name change in Poland and Slovakia C.I.8. a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	HU/H/0701/001-004/IB/001/G	yes	18.10.2021	17.11.2021	approval	no
A.2. b) for Nationally Authorised Products name change in HU	HU/H/0701/001-004/IB/002	yes	19.11.2021	19.12.2021	approval	no
A.2. b) for Nationally Authorised Products name change in ES From: Ezetimiba/Atorvastatina	HU/H/0701/001-004/IB/003	yes	30. 12. 2021		in process	no

Qualipharmacon 10 mg/10 mg, 10 mg/ 20 mg, 10 mg/ 40 mg, 10 mg/ 80 mg comprimidos recubiertos con película To: Ezetimiba/Atorvastatina Sandoz 10 mg/10 mg, 10mg/ 20 mg, 10 mg/ 40 mg, 10 mg/ 80 mg comprimidos recubiertos con película						