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# Public Assessment Report

**Name of the Product:**

## Torvazin Duo
## 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg
## hard capsules

## (atorvastatin/ezetimibe)

**Procedure number: HU/H/0593/001-003/DC**

**Marketing authorisation holder: EGIS Pharmaceuticals PLC**

**Date: 21 February 2020**

# CONTENT

# LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Torvazin Duo 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg hard capsules. The holder of the marketing authorisation is EGIS Pharmaceuticals PLC.

The active substances are atorvastatin (as atorvastatin calcium trihydrate) and ezetimibe. Each capsule contains 10 mg, 20 mg or 40 mg atorvastatin and 10 mg of ezetimibe.

The other ingredients in the core are: calcium carbonate, hydroxypropylcellulose, polysorbate 80, croscamellose sodium (SD711), sugar spheres (contain sucrose and maize starch), talc, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose (L-HPC B1), povidone K-25, sodium laurilsulfate, magnesium stearate

Capsule shell:
- 10 mg/10 mg hard capsules, capsule cap: titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172), gelatine
- 20 mg/10 mg hard capsules, capsule cap: titanium dioxide (E171), red iron oxide (E172), gelatine.
- 40 mg/10 mg hard capsules, capsule cap: titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172), gelatine.

Capsule body for all strengths: titanium dioxide (E171), yellow iron oxide (E172), gelatine

Appearance of the products:
- The 10 mg/10 mg hard capsules are unmarked self-closing size 0, hard gelatine capsule with caramel coloured cap and yellow coloured body, filled with pellets and a tablet.
- The 20 mg/10 mg hard capsules are unmarked self-closing size 0, hard gelatine capsule with reddish brown coloured cap and yellow coloured body, filled with pellets and a tablet.
- The 40 mg/10 mg hard capsules are unmarked self-closing size 0, hard gelatine capsule with dark brown coloured cap and yellow coloured body, filled with pellets and a tablet.

Capsule filling:
- Atorvastatin IR pellets: spheroidal shaped pellets.
- Ezetimibe 10 mg tablet: one piece of round, flat and bevel-edged, tablet with stylized E engraving on one side of the tablet and 612 engraving on the other side.

The hard capsules are marketed in OPA/Al/PVC//Al blister enclosed in folded cardboard box.

Torvazin Duo hard capsules (further on: Torvazin Duo) contains two different active substances in one capsule. One of the active substances is atorvastatin, belonging to the group of so called statins, the other active substance is ezetimibe.

Torvazin Duo is a medicine used to lower levels of total cholesterol, “bad” cholesterol (LDL cholesterol) and fatty substances called triglycerides in the blood. In addition, it also raises levels of “good” cholesterol (HDL cholesterol).

This medicine 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.

For most people, high cholesterol does not affect the way they feel because it does not produce any symptoms. However, if it is left untreated, fatty deposits can build up in the walls of the blood vessels causing them to narrow.

Sometimes, these narrowed blood vessels can get blocked which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. By lowering the cholesterol levels, the risk of having a heart attack, a stroke or related health problems can be reduced.

Torvazin Duo is used in patients whose cholesterol levels cannot be controlled by a cholesterol lowering diet alone. Patients should stay on their cholesterol lowering diet while taking this medicine.

The doctor may prescribe Torvazin Duo if the patient is already taking both atorvastatin and ezetimibe at the same dose level.

Torvazin Duo does not help the patients to lose weight.

**What patients need to know before taking Torvazin Duo**

Those patients should not take Torvazin Duo who:
- are allergic to atorvastatin, ezetimibe or any of the other ingredients of this medicine,
- have or have ever had a disease which affects the liver,
- have had any unexplained abnormal blood tests for liver function,
- are women able to have children and not using reliable contraception,
- are pregnant or trying to become pregnant,
- are breast-feeding,
- use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C.

*Warnings and precautions*

Before taking Torvazin Duo patients should discuss their doctor if they:
- have severe respiratory failure,
- 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 Torvazin Duo can lead to serious muscle problems (rhabdomyolysis),
- 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 or family history of muscle problems,
- have had previous muscular problems during treatment with other lipid lowering medicines (e.g. other "statin" or "fibrate" medicines),
- regularly drink a large amount of alcohol,
- have a history of liver disease,
- are older than 70 years.

Patients should contact their doctor promptly if experiencing unexplained muscle pain, tenderness, or weakness while taking Torvazin Duo. 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.

Patients should also tell their doctor if they have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.
While a patient is on this medicine, the doctor will monitor him/her closely if the patient has diabetes or is at risk of developing diabetes. The patient is likely to be at risk of developing diabetes if having high levels of sugars and fats in the blood, is overweight and has high blood pressure.

Patients should tell their doctor about all their medical conditions including allergies.

The combined use of Torvazin Duo and fibrates (medicines for lowering cholesterol) should be avoided since the combined use of Torvazin Duo and fibrates has not been studied.

*Children and adolescents*

The use of Torvazin Duo is not recommended in children and adolescents under the age of 18 years.

*Other medicines and Torvazin Duo*

Patient should inform their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

There are some medicines that may change the effect of Torvazin Duo or their effect may be changed by Torvazin Duo. 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":
- medicines used to alter the way the immune system works, e.g. ciclosporin;
- certain antibiotics, e.g. erythromycin, clarithromycin, telithromycin, rifampicin (medicines for bacterial infections);
- certain antifungal medicines, e.g. ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole;

- other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid derivatives, colestipol, colestyramine;
- some calcium channel blockers used for angina or high blood pressure, e.g., amlodipine, diltiazem;
- medicines to regulate the heart rhythm, e.g. digoxin, verapamil, amiodarone;
- medicines used in the treatment of HIV, e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, efavirenz, fosamprenavir, delavirdine, the combination of tipranavir/ritonavir, etc.;
- some medicines used in the treatment of hepatitis C (inflammation of the liver), e.g. telaprevir, boceprevir and the combination of elbasavir/grazoprevir;
- fusidic acid. If a patient needs to take oral fusidic acid to treat a bacterial infection, he/she will need to temporarily stop using this medicine. The doctor will tell them when it is safe to restart Torvazin Duo. Taking the latter medicine with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis).
- Other medicines known to interact with Torvazin Duo are:
    - warfarin, phenprocoumon, acenocoumarol or fluindione (medicines to prevent blood clots),
    - oral contraceptives,
    - stiripentol (an anticonvulsant medicine for epilepsy),
    - cimetidine (a medicine used for heartburn and peptic ulcers),
    - phenazone (a painkiller),
    - colchicine (used to treat gout),
    - antacids (indigestion products containing aluminium or magnesium),
    - St John's Wort (a medicine to treat depression).

*Torvazin Duo with food and alcohol*

Patients should note the following:

*Grapefruit juice*: patients should not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of Torvazin Duo.

*Alcohol*: drinking too much alcohol while taking this medicine should be avoided. See Section “Warnings and precautions” for details.

*Pregnancy and breast-feeding*

Patients should not take Torvazin Duo if they are pregnant, are trying to get pregnant or think they may be pregnant. Women of childbearing potential must not take Torvazin Duo, unless they use reliable contraceptive measures. If anybody gets pregnant while taking Torvazin Duo, she must stop taking it immediately and tell the doctor.

Those who are breast-feeding should not take Torvazin Duo.

The safety of Torvazin Duo during pregnancy and breast-feeding has not yet been proven. Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, should ask their doctor for advice before taking this medicine.

*Driving and using machines*

Torvazin Duo 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 it. If a patient gets dizzy, he/she should consult the doctor before driving or using machines.

*This medicine contains sucrose.*

Each Torvazin Duo 10 mg/10 mg capsule contains 13 mg, each Torvazin Duo 20 mg/10 mg capsule contains 26 mg and each Torvazin Duo 40 mg/10 mg capsule contains 51.5 mg sucrose. Those who have been told by their doctor that they have an intolerance to some sugars, should contact the doctor before taking this medicinal product.

**How to take Torvazin Duo**

Patients should keep on being on a low-cholesterol diet while taking Torvazin Duo.

The recommended daily dose for adults is one capsule of the given strength.

Torvazin Duo should be taken once daily.

The capsules can be taken at any time of day, with or without food. However, patients should try to take this medicine at the same time every day.

Each capsule should be swallowed whole with a drink of water.

Torvazin Duo is not suitable to start a treatment. Treatment initiation or dose adjustment if necessary should only be done by giving the active substances separately and after setting the appropriate doses the switch to Torvazin Duo of the appropriate strength is possible.

If the doctor has prescribed Torvazin Duo along with another medicine for lowering cholesterol containing the active ingredient colestyramine or any other medicine containing bile acid sequestrant, the patient should take Torvazin Duo at least 2 hours before or 4 hours after taking the bile acid sequestrant.

*What to do if more Torvazin Duo has been taken than it should have been?*

If a patient accidently takes too many capsules (more than the daily dose recommended by the doctor), the doctor or a nearest hospital should be contacted for advice.

*What to do if taking Torvazin Duo has been forgotten?*

If taking a dose has been forgotten, the patient should just take the next scheduled dose at the correct time. Double dose should never be taken to make up for a forgotten dose.

*May taking of Torvazin Duo be stopped by the patient?*

Those who want to stop taking Torvazin Duo should consult their doctor. The cholesterol levels might increase again when stopping it.

## Possible side effects

Like all medicines, Torvazin Duo can cause side effects, although not everybody experiences them.

If a patient experiences any of the following serious side effects or symptoms, should stop taking this medicine and tell the doctor immediately or should go to the nearest hospital accident and emergency department:
- 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 or rupture, or red-brown discolouration of urine and particularly, if at the same time the patient feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown (rhabdomyolysis). The abnormal muscle breakdown does not always go away, even after having stopped taking Torvazin Duo, and it can be life-threatening and lead to kidney problems;
- lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

If a patient experiences problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. The patient should consult the doctor as soon as possible.

*Other possible side effects*

Common (may affect up to 1 in 10 people):
- common cold (nasopharyngitis),
- allergic reactions,
- high levels of sugar in the blood,
- headache,
- throat pain,
- nosebleed,
- constipation,
- flatulence (excess gas in the intestinal tract),
- dyspepsia,
- feeling sick (nausea),

- diarrhoea,
- abdominal ache,
- muscle pain,
- joint pain,
- pain in arms and legs,
- muscle spasm,
- joint swelling,
- back pain,
- feeling tired (fatigue),
- elevations in some laboratory blood tests of muscle (CK) function,
- abnormal liver function test results, elevations in some laboratory blood tests of liver function (transaminases).

Uncommon (may affect up to 1 in 100 people):
- low levels of sugar in the blood,
- weight gain,
- decreased appetite,
- nightmare,
- sleeplessness,
- dizziness,
- numbness or tingling in the fingers and toes,
- reduction of sensation to pain or touch,
- taste disturbance,
- loss of memory,
- blurred vision,
- ringing in the ears,
- hot flush,
- high blood pressure,
- cough,
- vomiting,
- belching,
- inflammation of the pancreas, which causes a severe stomach pain which can extend to the back,
- heartburn,
- dry mouth,
- inflammation of the stomach (gastritis),
- inflammation of the liver (hepatitis),
- hives,
- itching,
- skin rash,
- hair loss,
- neck pain,
- muscle weakness,
- malaise (a feeling of overall weakness),
- asthenia (lack of energy and strength),
- chest pain,

- pain,
- swelling, especially in the hands and feet,
- fever,
- urine tests that are positive for white blood cells,
- increased level of a liver enzyme in the blood.

Rare (may affect up to 1 in 1,000 people):
- reduction in blood platelets, which increases the risk of bruising/bleeding (thrombocytopaenia),
- damage to the nerves of the legs and arms (such as numbness),
- visual disturbance,
- cholestasis (yellowing of the skin and the whites of the eyes),
- muscle disease with muscle weakness (myopathy),
- muscle inflammation,
- tendon injury.

Very rare (may affect up to 1 in 10,000 people):
- hearing loss,
- liver failure,
- breast enlargement in men (gynecomastia).

Not known (frequency cannot be estimated from the available data):
- depression,
- shortness of breath.
- muscle weakness that is constant (immune-mediated necrotizing myopathy).

Possible side effects reported with some statins are:
- sexual difficulties,
- breathing problems including persistent cough and/or shortness of breath or fever,
- diabetes. This is more likely if the patient has high levels of sugars and fats in the blood, is overweight and has high blood pressure. The doctor will monitor the patient while he/she is taking this medicine.

**How to store Torvazin Duo**

It should be stored below 30 °C in the original packaging in order to protect from moisture and should be kept out of the sight and reach of children.

# Scientific discussion

## during the initial phase

**This module reflects the scientific discussion for the approval of Torvazin Duo 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg hard capsules. The procedure was finalised at 24 July 2017. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

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

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Poland, Romania and the Slovak Republic) concerned the fixed combinations of atorvastatin/ezetimibe 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg hard capsules (Torvazin Duo hard capsules, named Torvazin Plus in Poland and Slovakia).

The marketing authorisation has been filed pursuant to Article 8(3), i. e. full-mixed application, of Directive 2001/83/EC, as amended.

Both active substances are well known with established clinical use.

Atorvastatin, an HMG-CoA reductase inhibitor, was initially launched in 1995 in the European Union. It 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 in 2002 in the European Union. 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.

To support the application, the applicant has submitted one pivotal bioequivalence study to demonstrate bioequivalence with two monocomponent preparations, frequently prescribed together to patients. These reference products were Sortis® 40 mg film-coated tablets (atorvastatin), manufactured by Pfizer GmbH and Ezetrol® 10 mg tablets (ezetimibe) manufactured by Schering-Plough Labo.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Torvazin Duo 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg hard capsules, from Egis Pharmaceuticals PLC.

The product is indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

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

# II. QUALITY ASPECTS

## II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Torvazin Duo 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg hard capsules via a decentralized procedure according to Article 8(3) of consolidated Directive 2001/83/EC (i.e. full dossier with all administrative, quality, pre-clinical and clinical data). The products have been developed by EGIS Pharmaceutical PLC.

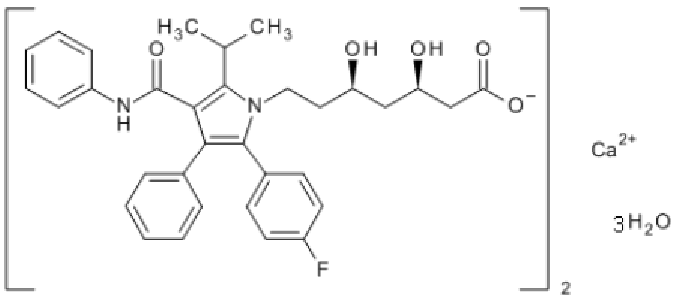
The applicant demonstrated bioequivalence with two monocomponent preparations, frequently prescribed together to patients. These reference products were Sortis® 40 mg film-coated tablets (atorvastatin), manufactured by Pfizer GmbH and Ezetrol® 10 mg tablets (ezetimibe) manufactured by Schering-Plough Labo.

## II.2 Drug substances

### *II.2.1 Atorvastatin calcium trihydrate*

Full documentation has been presented in the application dossier containing data on the quality and manufacture of the active substance. The Quality Overall Summary is adequate.

International Non-proprietary Name (INN): atorvastatin
Compendial name: atorvastatin calcium trihydrate
Chemical name: calcium (3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyr-rol-1-yl]-3,5-dihydroxy-heptanoate trihydrate
Structure:



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

Complete details of the manufacturing process have been presented. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by elemental analysis and the following spectroscopic methods: FT-IR, NMR ($^{1}$H-, $^{13}$C-NMR, 2D $^{1}$H - $^{1}$H and 2D $^{1}$H - $^{13}$C shift correlation) and MS (ES+, ES-). The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph, additional specification has only been set for residual solvent, residual metal, particle size distribution and polymorphic form. The specification reflects 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 European Medicines Agency (EMA) guideline on genotoxic impurities.

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

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable with the following storage restriction: “Store away from moisture. No restriction of temperature storage applies”.

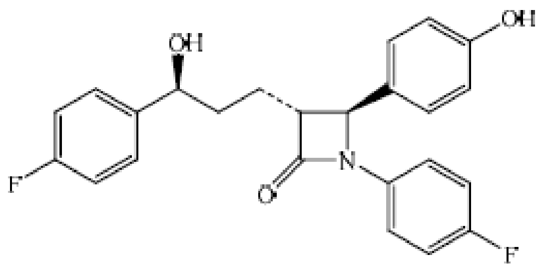
Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

### *II.2.2 Ezetimibe*

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedures. The Quality Overall Summary is adequate.

INN name: ezetimibe
Chemical name: 1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-azetidin-2-one

Structure:



The active substance is white to almost white crystalline powder, freely soluble in methanol and acetone, soluble in ethanol and practically insoluble in water. It shows polymorphism. The manufacturers consistently produce the correct isomer and the same polymorphic form.

The ASMF holders presented complete details of the manufacturing process. Description of the manufacturing processes of the drug substance is adequate.

Evidence of the structure has been confirmed by DSC, FT-IR, UV, $^{1}$H-NMR, $^{13}$C-NMR, MS and XRPD spectroscopy. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Ezetimibe is not official in the Ph. Eur., but it is included in the United States pharmacopoeia (USP). An in-house specification has been set for the active substance, which includes the following tests: description, identification by IR and chiral HPLC, specific optical rotation, water content, sulphated ash, related substances, diastereomeric impurity, residual solvents, assay as well as XRD (substance manufacturers). 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 the proposed re-test period is acceptable if stored in a tightly closed container.

GMP compliance of the drug substance manufacture is demonstrated by the applicant.

### II.3 Medicinal product

The aim was to develop hard capsules containing atorvastatin in the form of calcium trihydrate salt and ezetimibe as drug substances in 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg strengths, which are pharmaceutically equivalent and bioequivalent to the reference medicinal products Sortis® 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (atorvastatin calcium trihydrate, Pfizer) and Ezetrol® 10 mg tablet (ezetimibe, MSD).

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.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

- 10 mg/10 mg: unmarked self-closing, size 0, hard gelatine capsule with caramel coloured cap and yellow coloured body, filled with pellets and one tablet.
- 20 mg/10 mg: unmarked self-closing, size 0, hard gelatine capsule with reddish brown coloured cap and yellow coloured body, filled with pellets and one tablet.
- 40 mg/10 mg: unmarked self-closing, size 0, hard gelatine capsule with dark brown coloured cap and yellow coloured body, filled with pellets and one tablet.

Capsule filling:

- Atorvastatin IR pellets: spheroidal shaped pellets.
- Ezetimibe 10 mg tablet: one piece of round, flat and bevel-edged, tablet with stylized E engraving on one side of the tablet and 612 engraving on the other side.

The excipients used in the capsule filling are calcium carbonate, hydroxypropylcellulose, polysorbate 80, croscamellose sodium (SD711), sugar spheres (contain sucrose and maize starch), talc, mannitol, microcrystalline cellulose, low-substituted hydroxylpropyl cellulose (L-HPC B1), povidone K25, sodium laurilsulfate and magnesium stearate. Capsule shells contain titanium dioxide (E171), iron oxide (E172) (red/black/yellow) and gelatine.

All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on *the Products with the risk of TSE* has been demonstrated by the applicant.

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

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/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 30 months is approved with the following storage restriction: “Store below 30 °C in the original packaging in order to protect from moisture”.

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

### II.4 Discussion on chemical, pharmaceutical and biological aspects

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

From chemical-pharmaceutical points of view, the product is approvable.

# 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 Ecotoxicology/environmental risk assessment

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.

An environmental risk assessment is, therefore not deemed necessary.

## III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

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 pivotal bioequivalence study.

## IV.2 Pharmacokinetics

### *IV.2.1 Literature data*

*Absorption*

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations ($C_{max}$) 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.

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*

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

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

*Biotransformation*

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 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 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.

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 10day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

### *IV.2.2 Bioequivalence studies*

*Pivotal bioequivalence study*

To support the application, the applicant has submitted one pivotal bioequivalence study. The study was conducted between the atorvastatin/ezetimibe 40 mg/10 mg hard capsule (Test) and the concomitantly administered Sortis® 40 mg film-coated tablet (atorvastatin calcium trihydrate) and Ezetrol® 10 mg tablet (ezetimibe) under fasting conditions (Reference).

Biowaiver request was submitted for the lower strengths (10 mg/10 mg and 20 mg/10 mg hard capsules) according to the respective EMA bioequivalence guideline (general biowaiver criteria).

The results are shown in the following Tables.

Bioequivalence evaluation of plasma atorvastatin

| Pharmacokinetic parameter | Ratio T/R | 90% Confidence interval | Intrasubject variation CV% |
|---|---|---|---|
| $C_{max}$ | 107.19 | 96.88 – 118.61 | 43.7 |
| $AUC_{0-T}$ | 102.22 | 98.69 – 105.88 | 14.6 |

Bioequivalence evaluation of plasma free ezetimibe (parent compound)

| Pharmacokinetic parameter | Ratio T/R | 90% Confidence interval | Intrasubject variation CV% |
|---|---|---|---|
| $C_{max}$ | 107.94 | 100.38 – 116.07 | 30.6 |
| $AUC_{0-T}$ | 97.48 | 93.39 – 101.75 | 17.1 |

The results show that the 90% CI for the ln-transformed ratios of atorvastatin and free ezetimibe $C_{max}$ and AUC are within the bioequivalence range (80.00 – 125.00 %).

The other two strengths of capsules have the same qualitative compositions and are dose-proportional. They are manufactured according to the same manufacturing directions. The biovaiwer request is acceptable.

Both formulations were well tolerated, with no deaths or serious adverse events and no relevant differences in safety profiles were observed between the preparations. Test and reference products were comparable in their safety and tolerability.

*Possibility of pharmacokinetic interaction between the monocomponents:*

A discussion on the absence of potential pharmacokinetic interaction between the drug substances is provided in the Clinical Overview. Moreover, EGIS carried out a drug-drug interaction study with co-administration of atorvastatin and ezetimibe.

The study shows a similar bioavailability for atorvastatin between the two treatments with similar Treatment-A to Treatment-B ratios of geometric LSmeans and corresponding 90% confidence interval (CI) for $C_{max,ss}$ and AUC0-τ,ss. The result indicates that peak concentration and extent of exposure were similar when atorvastatin was given concomitantly with ezetimibe and when taken alone.

With regard to free ezetimibe, the co-administration of the active substances seems to have an impact on Treatment-A to Treatment-C ratios of geometric LSmean and the 90% CI for $C_{max,ss}$ and AUC0-τ,ss. Free ezetimibe peak concentration and extent of exposure were 30 and 20% higher when ezetimibe was co-administered with atorvastatin. However, the results presented for total ezetimibe show that both $C_{max,ss}$ and AUC0-τ,ss ratios of geometric LSmeans and the 90% CI were not affected by the co-administration of ezetimibe and atorvastatin.

Only free ezetimibe pharmacokinetics was affected by the co-administration *versus* ezetimibe alone. This interaction is considered to be negligible since free ezetimibe only account for a small proportion (10-20%) of total ezetimibe.

Consequently, the impact of free ezetimibe on the bioavailability of total ezetimibe seems minor, as bioavailability of total ezetimibe was comparable when ezetimibe was co-administered with atorvastatin and administered alone.

The results of this study support that co-administration of atorvastatin and ezetimibe does not significantly affect the pharmacokinetic profiles of the active substances.

## IV.3 Pharmacodynamics

Torvazin Duo contains atorvastatin and ezetimibe, two lipid-lowering compounds with complementary mechanisms of action. Torvazin Duo 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 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 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 guidelines CPMP/EWP/QWP/1401/98 Rev.1/Corr** and EMA/CHMP/158268/2017, 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 hard capsules 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.

12 completed 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.

**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 fixed-dose combination of atorvastatin and ezetimibe.

## IV.6 Pharmacovigilance

### *IV.6.1 Summary of the Pharmacovigilance System*

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

### *IV.6.2 Risk Management Plan*

*Summary of safety concerns*

| | |
|---|---|
| Important identified risks | • Rhabdomyolysis/myopathy<br>• Abnormal liver function<br>• Hypersensitivity<br>• Drug interaction with warfarin, another coumarin anticoagulant, or fluindione<br>• Drug interaction with ciclosporin |
| Important potential risks | • Cholecystitis/cholelithiasis<br>• Pancreatitis<br>• Hemorrhagic stroke<br>• Interstitial lung disease<br>• New-onset diabetes |
| Missing information | • Exposure during pregnancy and lactation<br>• Use in children less than 18 years of age<br>• Exposure in patients with moderate or severe hepatic insufficiency |

The summary list of safety concerns is aligned with that of similar products already authorised in order to harmonise the safety specification of essentially similar products in the European Union.

*Pharmacovigilance Plan*: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to EGIS products containing atorvastatin- ezetimibe combination. No additional activities are proposed.

*Risk Minimisation Measures*: routine measures (i.e. wording in the Summary of Product Characteristics, the Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to EGIS products containing atorvastatin-ezetimibe combination. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

### *IV.6.3 Periodic Safety Update Reports*

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## IV.7 Discussion on the clinical aspects

Torvazin Duo capsules are fixed combinations of atorvastatin (as atorvastatin calcium trihydrate) and ezetimibe.

They are indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

To support the application, the applicant has submitted one pivotal bioequivalence study to demonstrate bioequivalence with two monocomponent preparations, frequently prescribed together to patients. These reference products were Sortis® 40 mg film-coated tablets (atorvastatin), manufactured by Pfizer GmbH and Ezetrol® 10 mg tablets (ezetimibe) manufactured by Schering-Plough Labo.

From clinical points of view, the product is approvable.

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

## V.1 Summary

The present application concerns Torvazin Duo 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg hard capsules, fixed combinations of atorvastatin and ezetimibe. The applicant and the future holder of authorisation is EGIS Pharmaceuticals PLC.

They are indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

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

Concomitant use of the two active principles and its benefits have been proven by literature data. To support the application, the applicant has submitted one pivotal bioequivalence study to demonstrate bioequivalence with two monocomponent preparations, frequently prescribed together to patients. In another clinical study, it was proven that the pharmacokinetic interaction between the two active principles is negligible.

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 Torvazin Duo 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg hard capsules.

## V.2 Classification

Prescription-only medicine.

## V.3 Package Leaflet and user consultation

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

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

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

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

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