



BfArM

Bundesinstitut für Arzneimittel
und Medizinprodukte

Public Assessment Report

Decentralised Procedure

DE/H/3895/001-004/DC

**Atozet 10 mg/10 mg; 10 mg/20 mg; 10 mg/40 mg; 10 mg/80 mg
Filmdabletten**

DE/H/3896/001-004/DC

**Kexrolt 10 mg/10 mg; 10 mg/20 mg; 10 mg/40 mg; 10 mg/80 mg
Filmdabletten**

DE/H/3897/001-004/DC

**Orvatez 10 mg/10 mg; 10 mg/20 mg; 10 mg/40 mg; 10 mg/80 mg
Filmdabletten**

DE/H/3898/001-004/DC

**Tioblis 10 mg/10 mg; 10 mg/20 mg; 10 mg/40 mg; 10 mg/80 mg
Filmdabletten**

**Active substances:
Ezetimibe/Atorvastatin**

**Marketing authorisation holder in the Reference Member State,
Germany: MSD Sharp & Dohme GmbH**

Date: 15.05.2015

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Atozet®, Kexrolt®, Orvatez®, and Tioblis® 10/10, 10/20, 10/40, and 10/80 mg Filmtabletten, in the treatment of (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate and in adults with HoFH (for details please refer to SPC), is approvable

II. EXECUTIVE SUMMARY

II.1 Problem statement

These decentralised application procedures are according to Article 10(b) of Directive 2001/83/EC.

This decentralised procedure concerns a fixed dose combination of ezetimibe 10 mg and atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets. This application refers to the reference medicinal products Ezetrol® by Merck Sharp & Dohme Corp. and Lipitor® Film Coated Tablets by Pfizer Pharma.

With the DE as the Reference Member State in this Decentralised Procedure, MSD Sharp & Dohme GmbH is applying for Marketing Authorisations for Atozet, Kexrolt, Orvatez, and Tioblis 10/10, 10/20, 10/40, and 10/80 mg Filmtabletten (ezetimibe/atorvastatin called in this overview).

CMS:

DE/H/3895/001-004/DC: AT, BE; BG, CY, CZ, DK, EL, ES, FR, HR, HU, IE, IS, IT, LU, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK

DE/H/3896/001-004/DC: EL, ES, FR, IT

DE/H/3897/001-004/DC: BE, CZ, EL, ES, FR, IT, LU, PT, SK

DE/H/3898/001-004/DC: AT, ES

II.2 About the product

The active substance in the products is ezetimibe and atorvastatin calcium which are both used in monotherapy to lower the plasma cholesterol and serum lipids.

The ATC code is C10BA05

The indications claimed for are as follows:

Hypercholesterolemia

Ezetimibe/Atorvastatin is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

Ezetimibe/Atorvastatin contains ezetimibe and atorvastatin. Atorvastatin has been shown to reduce the frequency of cardiovascular events (see section 5.1). A beneficial effect of Ezetimibe/Atorvastatin or ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

Homozygous Familial Hypercholesterolaemia (HoFH)

Ezetimibe/Atorvastatin is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

II.3 General comments on the submitted dossier

The application is submitted in accordance with Article 10 (b) Directive 2001/83/EC as amended. The originator products of the mono-components in Germany are Ezetrol® 10 mg tablets, initially launched in 2002 in EU and Sortis® 10, 20, 40, and 80 mg film-coated tablets, approved in November 1996

The previously unknown fixed dose combination of ezetimibe and atorvastatin is considered a new active substance

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance Ezetimibe

Ezetimibe is not described in any pharmacopoeia. Complete information is provided for ezetimibe in module 3. The same drug substance is currently marketed in Ezetimibe Tablets and Ezetimibe/Simvastatin Tablets.

The manufacturing process has been adequately described. The proposed starting materials have been sufficiently justified and adequate controls are in place. A discussion regarding potentially genotoxic impurities -including those originating from the "starting materials"- and controls has been provided. In general adequate specifications and controls are in place for ezetimibe.

The proposed re-test period of 48 months when stored at or below 25°C in LDPE bags is justified.

Drug Substance Atorvastatin calcium trihydrate (form I)

Atorvastatin calcium trihydrate is described in the Ph.Eur. An ASMF has been provided by the ASMF holder for Atorvastatin calcium trihydrate (form I). The manufacturing process has been adequately described. The proposed starting materials are considered acceptable providing that the issue addressed in the restricted part of the ASMF AR is resolved.

Adequate specifications and controls are in place. Methods are adequately described and validated. The ASMF holder proposes a re-test period of 48 months without special storage conditions when stored in double PE bags within triple laminated bag in a HDPE container.

Drug Product

Ezetimibe/Atorvastatin FDC tablets (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg) have been designed to provide robust, physically and chemically stable solid oral dosage forms containing 10 mg of Ezetimibe and 10 mg, 20 mg, 40 mg, or 80 mg of Atorvastatin that are bioequivalent to the marketed Ezetimibe and Atorvastatin Calcium Mono-tablets.

The manufacture of the Ezetimibe/ Atorvastatin FDC tablets is considered as a common standard process by granulation of each API, compression of the bilayer tablet and film-coating and has been described in sufficient detail. The manufacturing process and in-process controls correspond to the

actual standards of pharmaceutical technology and are suitable to guarantee an appropriate quality of the finished product.

Acceptable validation data on overall 12 validation scale batches have been provided. The Common excipients of acceptable quality are utilised. Release and shelf-life specifications are acceptable.

The analytical in-house methods have been sufficiently described and validated in line with ICH guidelines.

The batch analyses data together with the results obtained from the stability testing confirm consistency and uniformity of the product based on the parameters tested and indicate the reproducibility of the manufacturing process for the drug products.

The presented primary packaging system for marketing, Al/Al- blister, is standard for solid oral formulations. The provided specifications and information for the proposed container closure system are considered as sufficient for the intended use.

Data of stability testing in accordance with ICH requirements at long-term (30°C/75% RH) and accelerated conditions have been provided. The tablets are packed in the blisters for the market (with nitrogen blanket). Stability results for both tested tablet strengths are comparable and remain well within their specified limits.

Non-clinical aspects

Atorvastatin is a well-known potent HMG- CoA reductase inhibitor, whereas ezetimibe is a well-known potent inhibitor of cholesterol absorption. Additive effects of the combination in the reduction of hypercholesterolaemia or hyperlipidaemia was demonstrated in the past. Ezetimibe was approved nationally in Germany in 2002 with a subsequent mutual recognition procedure (DE/H/0396/001). No additional pharmacodynamics studies were provided and no further studies are considered necessary.

No new pharmacokinetic studies were provided by the applicant. The applicant refers instead to the data submitted for the approval of the active substances ezetimibe and atorvastatin. Additional pharmacokinetic data was obtained by toxicokinetic studies supporting the marketing authorisation of the ezetimibe in combination with statin (including atorvastatin).

Ezetimibe is extensively conjugated to ezetimibe glucuronide whereas atorvastatin is rapidly metabolised to ortho-hydroxy-atorvastatin and para-hydroxy-atorvastatin. Systemic exposure of both active substances increased with dose, but pharmacokinetic interactions have been observed at higher doses. The underlying mechanism was not established at the time point of the initial submission and the applicant provides no further explanation. Since clinical study data does not show a clinically relevant pharmacokinetic interaction further studies are not considered necessary.

The repeated dose toxicity of the combination of ezetimibe with atorvastatin was investigated in rats and dogs. The data was submitted in the past in support of the marketing authorization for ezetimibe with statins including atorvastatin. The toxicological findings, including target organ identification, following co-administration of ezetimibe with a statin are typically those seen with statins/atorvastatin alone. It was agreed, that the more pronounced effects seen in co-administration studies compared to statins alone are likely caused by pharmacokinetic and dynamic interactions.

The reproductive toxicity was investigated in rats and rabbits. The co-administration of ezetimibe with atorvastatin resulted in a 12.4 fold increase in conjugated ezetimibe values. Caudal vertebra malformations were found in three rabbit studies where ezetimibe had been co-administered with atorvastatin. These findings were not present in the facilities historical control and are therefore attributed to the administration of the test articles. In the rat studies no malformations were observed. The use of statins is generally contraindicated in pregnant women, as congenital malformations have been reported for children prenatally exposed to HMG-CoA-reductase inhibitors. Therefore, ezetimibe in combination with a statin is contraindicated in pregnant women as well.

An ezetimibe/atorvastatin combination was tested in a standard battery for genotoxicity meeting the requirements of ICH S2(R1) guideline. All tests gave negative results.

Carcinogenic potential of ezetimibe/atorvastatin fixed combination was not evaluated in 2 year

bioassays in mouse or rat. Life time bioassay had been conducted with the individual compounds ezetimibe and atorvastatin for the individual market authorizations. Ezetimibe did not cause increase in neoplastic lesions in mouse or rat. Atorvastatin caused liver adenoma and carcinoma in high dose groups in mouse (at 6 times the human AUC at 80 mg/d human dose). This pattern however is not uncommon for statins and has so far not been considered of clinical relevance. In rat two different rare tumours in muscle were found in high dose females (at 16 times the human AUC at 80 mg/d human dose) without statistical significance and questionable treatment relation. There is no evidence that the combination of the substances would exhibit different target organs or unexpected additive or over-additive adverse reactions.

Impurities and degradation products specified in the ezetimibe/atorvastatin fixed combination product are considered sufficiently qualified from the toxicological point of view.

The non-clinical sections of the SmPC and PIL are adequate.

III.2 Clinical aspects

Pharmacokinetics

In support of the application for a fixed dose combination ezetimibe and atorvastatin formulation 2 bioequivalence studies under fasting conditions have been performed with the lowest strength 10 mg/10 mg and the highest strength 10 mg/80 mg. In addition the applicant performed 1 food effect study with the highest strength 10 mg/80 mg.

P391 was a single-dose, full replicate, comparative bioavailability study of two formulations of ezetimibe/atorvastatin calcium 10 mg/10 mg FDC tablets vs. Ezetrol® 10 mg (Reference by Merck Sharp & Dohme Limited, United Kingdom) administered with Lipitor® 10 mg (Reference by Pfizer Limited, United Kingdom) in healthy volunteers under fasting condition with a washout period of 14 days between successive drug administrations.

The study design, analytical methodology and statistical evaluation of the bioequivalence study for the FDC were appropriately designed and conducted in compliance with the recommendations of the relevant guidelines for GCP and GLP.

The primary variables for conclusion of bioequivalence were AUC_{0-t} and C_{max} for the total ezetimibe, unconjugated ezetimibe and parent compound atorvastatin. Criteria for conclusion of bioequivalence was defined that the 90% confidence interval for the test/reference LSM ratio of the log-transformed AUC_{0-t} should be between 80-125% for atorvastatin and the 90% confidence interval for the test/reference LSM ratio of the log-transformed C_{max} should be widened to a maximum range of 69.84–143.19% dependent on the intra-subject variability for C_{max}. Based on the data of study P391 the 90% confidence intervals for the log-transformed primary variables AUC_{0-t} and C_{max} for total ezetimibe, unconjugated ezetimibe and atorvastatin were within the acceptance range of 80-125%. Therefore, the test and reference products can be considered bioequivalent.

The Applicant conducted a second bioequivalence study which was a single-dose, full replicate, comparative bioavailability study of two formulations of ezetimibe/atorvastatin calcium 10 mg/80 mg FDC tablets vs. Ezetrol® 10 mg (Reference by Merck Sharp & Dohme Limited, United Kingdom) administered with Lipitor® 80 mg (Reference by Pfizer Limited, United Kingdom) in healthy volunteers under fasting condition with a washout period of 14 days between successive drug administrations (study P392).

The study design, analytical methodology and statistical evaluation of the bioequivalence study for the FDC were appropriately designed and conducted in compliance with the recommendations of the relevant guidelines for GCP and GLP.

The primary variables for conclusion of bioequivalence were AUC_{0-t} and C_{max} for the total ezetimibe, unconjugated ezetimibe and parent compound atorvastatin. Criteria for conclusion of bioequivalence was defined that the 90% confidence interval for the test/reference LSM ratio of the log-transformed AUC_{0-t} should be between 80-125% for atorvastatin and the 90% confidence interval for the test/reference LSM ratio of the log-transformed C_{max} should be widened to a maximum range of 69.84–143.19% dependent on the intra-subject variability for C_{max}.

Based on the data of study P392 the 90% confidence intervals for the log-transformed primary variables AUC_{0-t} and C_{max} for total ezetimibe, unconjugated ezetimibe and atorvastatin were within the acceptance range of 80-125%. Therefore, the test and reference products can be considered bioequivalent.

Several information according to the validation method and statistical methods could not be located in the dossier and the MAH was requested to submit these information with the D106 response. All these information were provided.

On request the applicant provided the dissolution profiles of the 4 strengths in the different media as requested and also the associated plots.

The dissolution data of the 10 mg/10 mg biobatch tablets were compared with the ones of the 10 mg/20 mg tablets, and the 10 mg/ 80 mg biobatch tablets were compared with the ones of the 10 mg/40 mg tablets in four media: the proposed QC media (pH 6.8 phosphate buffer with 0.2% Tween 80), buffers at pH 6.8 and 4.5, and simulated gastric fluid (SGF) pH 1.2, respectively. The profiles demonstrate that the f₂ values were within the range of 50 – 100 or both profiles show > 85% in 15 minutes. Only for atorvastatin the 10 mg/40 mg and 10 mg/80 mg were not similar in single tablet comparison in SGF and pH 4.5 buffers which was charged to non-sink conditions of atorvastatin at the 10 mg/80 mg tablet strength in these media and this was addressed by demonstrating the similarity profile of two 10 mg/40 mg tablets compared to the 10 mg/80mg tablet strength, according to the Guideline for Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1).

To proof the impact of food on the FDC the applicant conducted a food effect study as an evaluation of the comparative bioavailability of ezetimibe/atorvastatin calcium 10 mg/80 mg FDC tablets (Merck Sharp & Dohme Corp., USA) after a single-dose in healthy subjects under fasting and fed conditions.

Results of the food effect study demonstrate that the systemic exposure of atorvastatin is nearly similar under fasting and fed conditions while the plasma concentration is about 7% lower under fed conditions. T_{max} is 1 hour under fasting and 2.25 hours under fed conditions.

For unconjugated ezetimibe both rate and extend of absorption are similar under fasting and fed conditions. T_{max} is doubled, 0.75 hours under fasting and 1.5 hours under fed conditions.

For total ezetimibe the systemic exposure is similar under fasting and fed conditions while the plasma concentration is about 15% higher under fed conditions compared to fasting conditions. T_{max} is 0.75 hours under fasting and 1.25 hours under fed conditions.

The changes of magnitude in AUC and C_{max} when ezetimibe/atorvastatin 10 mg/80 mg FDC was dosed with a high-fat, high-calorie food are not considered to be clinically meaningful. The ezetimibe/atorvastatin FDC can be administered with or without food.

Pharmacodynamics

N/A

Clinical efficacy

To demonstrate the efficacy of ezetimibe/atorvastatin FDC the applicant provided 12 ezetimibe + atorvastatin co-administration studies, classified as factorial studies, add-on studies, add-on titration studies, long term studies, and special population studies. 7 of these studies were previously included in the original marketing application for ezetimibe and five additional studies have been completed since the original application for ezetimibe. Original studies for Marketing Application (ezetimibe) were studies P00692, P00693, P01030, P01417, P01418, P02154, and P02173/P2246. Additional co-administration studies completed since the original marketing application were studies P040, P079, P090, P112, and P162.

The studies provided by the applicant demonstrate the increased LDL-C-lowering effects of ezetimibe + atorvastatin versus atorvastatin monotherapy. Co-administration of ezetimibe + atorvastatin pooled across all doses lead to about 12.1% increased reduction in LDL-C. It could also be demonstrated that the addition of ezetimibe to an ongoing atorvastatin monotherapy lead to greater LDL-C reductions than those produced with the addition of placebo or doubling the dose of

atorvastatin. Reducing effects on other lipid parameter than LDL-C could also be shown for the ezetimibe + atorvastatin combination therapy. With the co-administration of ezetimibe to atorvastatin a greater LDL-C lowering was established and more patients could attain their LDL-C goals.

Clinical safety

The adverse events profiles of ezetimibe and atorvastatin are well established. The 2 BE studies P391 and P392 did not show differences in relation to safety between the test and reference products.

The applicant provided post-marketing data of ezetimibe co-administered with atorvastatin which did not lead to new safety findings which are not addressed in the reference CCDS for both ezetimibe and atorvastatin. The adverse events profile is similar to that of the monotherapies. Particularly no increased risk of hepatic aminotransferase elevations, muscle toxicity or CPK elevation compared to atorvastatin monotherapy was detected. The benefit-risk ratio seems to be positive.

As the MAH has approved an ezetimibe/atorvastatin FDC (Liptruzet®) outside the EU in May 2013 which is available on the market, the MAH submitted post-marketing data of this medicinal product. 76 events in 39 post-marketing cases were submitted from health care providers. 2 of this events were expected to be serious, 1 case of dysgeusia in a 45 year old male patient and 1 case of pyelonephritis in a 55 year old female patient. Both patients recovered. While dysgeusia is listed in the SOC Nervous system disorders of atorvastatin, pyelonephritis is not listed yet (see D120 clinical AR). No new safety signals are suggested. The MAH is requested to closely monitor these adverse events.

On request of CMS PT on Day 100 responses the MAH submitted data from a randomized, investigator/evaluator blind, placebo-controlled, single-center, multiple-dose, parallel-group study in healthy hypercholesterolemic female and male subjects (N=32; 8 subjects per treatment group) regarding potential PK interaction between ezetimibe and atorvastatin. The primary objective of the study was to evaluate the safety, tolerability and pharmacodynamic effects of the co-administration of ezetimibe and atorvastatin in this population. Even that the sample size of 32 subjects was small the results show that there was no significant clinical pharmacokinetic drug interaction between atorvastatin and ezetimibe.

Finally the MAH followed a request of the RMS to add a note in section 4.5 of the SPC according to the SPC of the originator of atorvastatin, Lipitor® regarding the increased risk of myopathy/rhabdomyolysis in case of concomitant use of ezetimibe and atorvastatin.

Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH'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 and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

At the start of this DCP the applicant submitted the first new Risk Management Plan (Version 1.0, signed off 05-Sept-2013) for ezetimibe/atorvastatin FDC in four different dose strengths (10/10mg, 10/20mg, 10/40mg and 10/80mg). This new Risk Management Plan was subsequently updated to Version 2.0 (signed off 04-April-2014) and to Version 3.0 (signed off 10-July-2014) according to the comments raised by RMS and CMSs. With the Day201-response the applicant included the missing reference to Part VI and VII in the Table of Contents which was erroneously not included. The RMP is now acceptable:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Rhabdomyolysis/myopathy	Rhabdomyolysis/myopathy is	None

	considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.4, 4.8; PIL sections 2, 4).	
Abnormal liver function	Abnormal liver function is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.2, 4.3, 4.4, 4.8; PIL sections 2, 4).	None
Hypersensitivity	Hypersensitivity is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.3, 4.8; PIL sections 2, 4).	None
Interstitial lung disease	Interstitial lung disease is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.4, 4.8; PIL section 4).	None
New-onset diabetes	New-onset diabetes is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.4, 4.8; PIL sections 2, 4).	None
Important potential risk		
Cholecystitis/cholelithiasis	Cholecystitis/cholelithiasis is considered to be adequately addressed in the currently proposed SmPC (SmPC section 4.8; PIL section 4).	None
Pancreatitis	Pancreatitis is considered to be adequately addressed in the currently proposed SmPC (SmPC section 4.8; PIL section 4).	None
Haemorrhagic stroke	Hemorrhagic stroke is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.4, 5.1; PIL sections 2, 4).	None
Malignancies	Ongoing monitoring of post-marketing and clinical trial data to determine true risk of malignancy with drug exposure.	None
Missing information		
Exposure during pregnancy and lactation	Exposure during pregnancy is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.3, 4.6; PIL section 2).	None
Use in children less than 18 years of age	Use in children is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.2, 5.2; PIL section 2).	None
Use in patients with moderate or severe hepatic insufficiency	Exposure in patients with moderate or severe hepatic insufficiency is considered to be adequately addressed in the currently proposed SmPC (SmPC sections 4.4, 5.2; PIL section 2).	None

Periodic Safety Update Report (PSUR)

According to the EURD list the mono-components of this FDC (ezetimibe and atorvastatin) have a PSUR submission cycle of 3 years and these products have a well-known safety/efficacy profiles and therefore the RMS considers that the same PSUR submission frequency of 3 years applies also this FDC. The applicant can submit the PSURs starting with 3-years cycle. Further to the granting of

the MA the RMS will apply for inclusion of this combination in the EURD-list with a PSUR cycle of 3 years.

IV. BENEFIT RISK ASSESSMENT

The benefit risk assessment is favourable and a marketing authorisation can be granted.