THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CHOLVAT (ATORVASTATIN (AS ATORVASTATIN CALCIUM TRIHYDRATE 40 MG) FILM COATED TABLETS

Version number 01, 06/01/2023

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1. Introduction

Atorvastatin is a selective, competitive inhibitor of HMGCoA reductase, the rate-limiting enzyme responsible for the conversion of 3‑hydroxy-3‑methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including ~~cholesteronn.~~

The product is indicated for:

Hypercholesterolaemia
Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDLcholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (LDL apheresis) or if such treatments are unavailable.

Prevention of cardiovascular disease
Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event (see SmPC section 5.1), as an adjunct to correction of other risk factors.

A comprehensive description of the indications and posology is given in the SmPC.

1.1.Product details

Registration number	TAN 22 HM 0501
Brand name	Cholvat 40 mg film-coated tablets
Generic name, strength and form	Each film-coated tablet contains 40 mg of atorvastatin as atorvastatin calcium trihydrate
ATC classification	Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05
Distribution category	POM
Country of origin	Spain
Associated product	The finished product is presented as a film-coated tablet containing ~~20 mg~~ of atorvastatin as active substance

Marketing Authorization Holder	B&O PHARM ZAC de la Masquère, 500 rue de l'Hers, 31750 ESCALQUENS, France
Local Technical Representative	Tridem Pharma Tanzania Limited P.O Box 23145, Plot No. 70, Keko-Mwanga Dar es Salaam

1.2.Assessment procedure

The application for registration of Cholvat 40 mg film-coated tablets was submitted on 15/06/2021. The product underwent abridged assessment. Assessment was completed in one round of evaluation. Cholvat 40 mg film-coated tablets was registered on 05/12/2022.

1.3.Information for users

Visual description of the finished product	Round, biconvex film-coated tablets with bisection line on one side and debossed 40 on other side
Primary packing material	Pack of 3 x 10's in Alu-Alu blister pack
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	24 months Do not store above 30°C
Route of administration	Oral
Therapeutic indications	Cholvat 40 mg film-coated tablets are indicated for treatment Hypercholesterolaemia, prevention of cardiovascular disease and reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are

2. Labelling and product information

Summary of product characteristics

The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet

The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Cholvat 40 mg film-coated tablets

Composition: Each film-coated tablet contains 40 mg of atorvastatin as atorvastatin calcium trihydrate

Pack size: 3 x 10's tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C

Manufacturer address: LABORATORIOS LICONSA, S.A Avda. Miralcampo 7, Polígono Industrial Miralcampo 19200, Azuqueca de Henares Guadalajara, Spain

Unique identifier: N/A

Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:

Brand name and strength: Cholvat 40 mg film-coated tablets

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: LABORATORIOS LICONSA, S.A Avda. Miralcampo 7, Polígono Industrial Miralcampo 19200, Azuqueca de Henares Guadalajara, Spain

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Special warnings/precautions or instructions for use: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Mock labels are appended as annex I. (Requested)

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of CEP

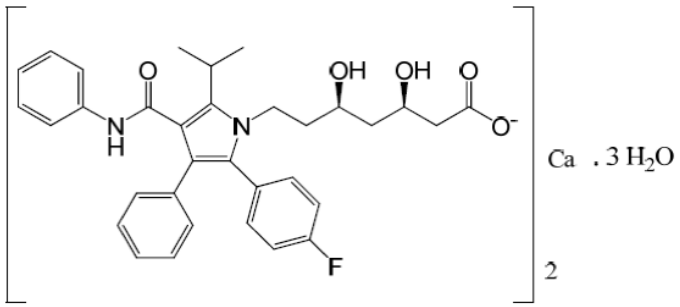
General properties
Atorvastatin calcium (as trihydrate) API is compendia in USP and BP Pharmacopeia.

Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10}$

Chemical names:
Calcium (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenyl carbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyhepatanoate trihydrate

(βR,δR)-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium trihydrate

Structure:



Critical physico-chemical properties are:
The active substance is atorvastatin calcium (as trihydrate), an established active substance described in the European Pharmacopoeia (Ph.Eur.)/USP. It is a white or almost white powder, which is practically insoluble in water, slightly soluble in ethanol and practically insoluble in methylene chloride. Polymorphic form I is used. Atorvastatin calcium exhibits isomerism having a chiral carbon at the three and five position of its structure (R-isomer)

Manufacture
Two different manufacturers (MSN Pharmachem Private Limited, Plot No.: 212 / A, B, C, D, Phase-II, IDA Pashamylaram, Pashamylaram (Village), Patancheru (Mandal), Sangareddy District, Telangana, India and Zhejiang Jiangbei Pharmaceutical Co., Ltd, Dongdai Village Zhang'an Street, Jiaojiang, Taizhou, Zhejiang, China). For both

manufacturers, the CEP procedure was used for the active substance. CEPs have been submitted; therefore, no details on the manufacturing process have been included. The manufacturing facilities were noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by_____. Atorvastatin calcium (as trihydrate) API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per ~~in-house~~ standards and ICHQ3A. The parameters monitored during quality control are: appearance, identity (IR), assay (HPLC), sodium content, related substances (HPLC), Enantiomeric purity (HPLC), residual solvents (GC), water content (KF) and particle size. The specification is considered acceptable. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The active substance is stable for 36 months (manufacturer-I) and manufacturer-II) when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM

Quality of the Finished Pharmaceutical Product

Formulation

Cholvat 40 mg film-coated tablets is presented as Round, biconvex film-coated tablets with bisection line on one side and debossed 40 on other side.

Cholvat 40 mg film-coated tablets contains Calcium carbonate, Cellulose Microcrystalline, Lactose monohydrate, Croscarmellose sodium Copovidone VA64, Crospovidone Type B, Magnesium stearate, Sodium lauril sulfate, Silica, colloidal anhydrous Talc. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Film coating: Hypromellose E464 Macrogol 400 Titanium dioxide, E171

Manufacture

The finished product was manufactured at LABORATORIOS LICONSA, S.A Avda. Miralcampo 7, Polígono Industrial Miralcampo 19200, Azuqueca de Henares

Guadalajara, Spain. The compliance of the site to TMDA GMP standards was confirmed through desk review

Specifications

The FPP is compendia in BP. The manufacturer controls the quality of the finished product as per European Pharmacopoeia (Ph.Eur.) standards and ICH requirements. The parameters monitored during quality control are: description, identification, (also for colorant), average mass, uniformity of dosage units (content uniformity), dissolution, assay, related substance and microbiological quality. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30 ± 2°C & 75% ± 5% RH for 18 months and 40 ± 2°C & 75% ± 5% RH for 6 months. All stability results met the set requirements and a shelf-life of 24 months is considered acceptable.

Safety and efficacy information

The Bio-equivalence study was carried out on atorvastatin 80 mg film-coated tablets. Based on acceptable Bioequivalence study for atorvastatin 80 mg film-coated tablets, a bio-waiver was requested for atorvastatin 40 mg film-coated tablet. The biowaiver was approved based on additional strength. In relation to the strength biowaiver, comparative dissolution study of Test product 40mg film-coated tablets batch no. 30510 0810 versus bio-batch product 80 mg film-coated tablets batch no.30528 0710 was performed at three selected media. The study demonstrated similarity of the dissolution profiles and thus from this point of view the biowaiver has been accepted.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics Cholvat 40 mg film-coated tablets is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

成品名称： Product Name	阿托伐他汀钙片40mg Atorvastatin calcium tablets 40mg
版本 Version	B&O CHEMO (LICONSA)版
物料名称 Packing Material	小盒 Small box
尺寸： Dimensions	62*21*76 mm
材质： Substance	
包材编码 Artwork No/ LICONSA	
修改编号： No. / B&O	33#2020
修改内容： Modify / B&O	新增包装设计
制作：陆倩婷 日期：2020.3.10	

色标：

- CMYK:0/0/0/100
- CMYK:0/100/100/0
- CMYK:0/60/30/0
- CMYK:0/50/100/0
- CMYK:40/100/100/0