COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Fluvastatine Aurobindo SR 80 mg, prolonged-release tablets (fluvastatin sodium)

## NL/H/6006/001/DC

## Date: 30 October 2024

**This module reflects the scientific discussion for the approval of Fluvastatine Aurobindo SR 80 mg, prolonged-release tablets. The procedure was finalised at 12 June 2008 in Denmark (DK/H/1217/001/DC). After a transfer on 2 September 2024, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| RMS | Reference Member State |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fluvastatine Aurobindo SR 80 mg prolonged-release tablets, from Aurobindo Pharma B.V. The date of authorisation was on 2 March 2009 in Denmark.

The product is indicated for:
Dyslipidaemia
Treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.
Secondary prevention in coronary heart disease
Secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary intervention.

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

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Lescol 80 mg prolonged-release tablets, which has been registered in UK by Novartis Healthcare A/S since 1993. The reference product in Denmark is Lescol 80 mg prolonged-release tablets, Novartis Healthcare A/S.
The reference product used to show bioequivalence is Locol 80 mg prolonged-release tablet, Novartis Pharma GmbH, from the German market.

The marketing authorisation is granted based on article 10.1 and 10.3 of Directive 2001/83/EC due to differences in the approved indications for the brand-leader in the respective MS.

Fluvastatin, a fully synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol.

This product was originally authorised in several Members States of the European Union under the decentralised procedure DK/H/1217/001/DC with Denmark as RMS. Subsequently, the procedure was split and RMS transfers to the UK (UK/H/6827/001/DC) and for the EU to Portugal (PT/H/2038/001/DC ) took place. The current RMS in the EU is the Netherlands.

# II. QUALITY ASPECTS

## II.1 Introduction

Fluvastatine Aurobindo SR 80 mg prolonged-release tablets contain as active substance 80 mg of fluvastatin (as fluvastatin sodium).

The tablet is a yellow, round, biconvex tablet embossed with “F” on one side.

Fluvastatine Aurobindo SR is packed in blisters (OPA/Alu/PVC-Alu); HDPE bottles with desiccant and snap-on cap (LDPE) with a tamper evident ring and round, brown glass containers closed with rubbed plastic cap (HDPE) with thread including seal. Desiccants are HDPE plastic canisters filled with activated silica gel.

The excipients in the tablet core are: Povidone; microcrystalline cellulose; hydroxyethyl cellulose; mannitol and magnesium stearate.
The film-coating consists of: Hypromellose 50; macrogol 6000; iron oxide yellow (E172) and titanium dioxide (E171).

Compliance wih Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

## II.2 Drug Substance

The active substance fluvastatin sodium is not described in the European Pharmacopoeia (Ph.Eur) but a draft Ph.Eur. monograph exists and the substance is monographed in the USP. Two different sources of active substance are proposed. The documentation for both sources is provided in the form 3/7 of EDMFs. Fluvastatin sodium is a chiral molecule possessing two chiral centres. The substance displays polymorphism.

Manufacturing process
Synthesis has been satisfactorily described from well defined starting materials.

Quality control of drug substance
Analytical methods have been properly described and validated.

Stability of drug substance
Stability studies are provided to support a proposed retest period of 24 months when stored at 2°C-8°C.

### II.3 Medicinal Product

Pharmaceutical development
The product composition is properly described. The pharmaceutical development has been explained and all excipients justified. Dissolution method development has been adequately explained and shown to be discriminatory. Suitable dissolution profile data are provided.

Manufacturing process
Pilot scale batches have been validated and stability tested.

Quality control of drug product
Bioequivalence testing has been conducted with one of the pilot scale batches. Two different manufacturing sites have been proposed and validation data are provided from both sites in support of this.

Stability of drug product
The finished product release and shelf-life specifications have been drawn up in accordance with general Ph.Eur. and ICH requirements and cover appropriate parameters for this dosage form. The analytical methods have been adequately described and validated.

Stability data are provided covering a period of up to 18 months at 25°C/60% RH in three proposed market packs (AL blister, HDPE container and glass container) together with up to 6 months at 40°C/75% RH. Testing intervals are in accordance with ICH recommendations. The proposed shelflife period of 24 months with no particular temperature storage precaution can be accepted. The product however should be stored in the original pack to protect from light as photostability testing indicates a sensitivity to visible light. In-use stability has been evaluated and the tablets found to be adequately stable.

## III. NON-CLINICAL ASPECTS

This product is a generic formulation of Lescol prolonged-release tablets, which is available on the European market. Pharmacodynamic, pharmacokinetic and toxicological properties of fluvastatin are well known. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application. An overview based on a literature review is therefore appropriate.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Fluvastatin is a well-known active substance with established efficacy and tolerability.

The following 3 types of BE studies, required in agreement with the EU guideline on bioeguivalence on modified-release products, have been performed:

- A single dose fasting study
- A single dose fed study
- A multiple-dose fasting study

## IV.2 Pharmacokinetics

For this generic application, the MAH has submitted 3 bioequivalence studies in which the pharmacokinetic profile of the test product Fluvastatine Aurobindo SR 80 mg prolonged-release tablets is compared with the pharmacokinetic profile of the reference product Lescol 80 mg prolonged-release tablets, Novartis Pharma GmbH, from the German market.

Bioequivalence studies

*SINGLE DOSE FASTING STUDY*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 19-55 years. Each subject received a single dose (80 mg) of one of the 2 fluvastatin formulations. The tablet was orally administered with 240 ml water after at least 10 hours of fasting. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dosing and at 0.5, 1.00, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10, 12, 16 and 24 hours after administration of the products.

*Results*

2 subjects dropped out of the study (one subject did not show up for period 2, another subject withdrew for personal reasons). Both were excluded from the statistical analysis. 48 subjects were eligible for pharmacokinetic analysis.

**SUMMARY OF RESULTS**
**(+)-3R,5S-FLUVASTATIN**
**N = 48**

**Pharmacokinetic Parameters**

| Parameters | | Test (Fluvastatin Sodium (A)) Mean | ± | SD | CV (%) | Reference (Locol (B)) Mean | ± | SD | CV (%) |
|---|---|---|---|---|---|---|---|---|---|
| $AUC_{0-t}$ | (ng·h/mL) | 133.29 | ± | 59.89 | 44.94 | 118.13 | ± | 52.97 | 44.84 |
| $AUC_{0-inf}$ * | (ng·h/mL) | 144.58 | ± | 62.87 | 43.48 | 132.81 | ± | 60.78 | 45.77 |
| $C_{max}$ | (ng/mL) | 28.30 | ± | 13.85 | 48.94 | 30.60 | ± | 12.75 | 41.66 |
| Residual Area* | (%) | 3.66 | ± | 2.32 | 63.54 | 8.03 | ± | 6.19 | 77.15 |
| $T_{max}$ | (h) | 3.10 | ± | 1.65 | 53.27 | 2.98 | ± | 2.16 | 72.61 |
| $T_{max}$ ** | (h) | 3.00 | ± | 2.00 | - | 2.50 | ± | 1.13 | - |
| $K_{el}$ * | ($h^{-1}$) | 0.2167 | ± | 0.0959 | 44.24 | 0.1428 | ± | 0.0927 | 64.90 |
| $T_{½ el}$ * | (h) | 3.93 | ± | 1.96 | 49.75 | 6.37 | ± | 2.89 | 45.35 |

* For these parameters, N = 33.
** Medians and interquartile ranges are presented.

**Fluvastatin Sodium (A) vs Locol (B)**

| | $AUC_{0-t}$ | $AUC_{0-inf}$ * | $C_{max}$ |
|---|---|---|---|
| Ratio[1] | 113.31% | 109.98% | 90.30% |
| 90 % Geometric C.I.[2] | 104.12 % to 123.32 % | 97.88 % to 123.57 % | 81.72 % to 99.77 % |
| Intra-Subject CV | 24.69 % | 27.27 % | 29.28 % |

[1] Calculated using least-squares means according to the formula: $e^{(\text{Fluvastatin Sodium (A) - Locol (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data
* For this parameter, N = 33.

*SINGLE DOSE FED STUDY*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 164 healthy male subjects, aged 18-55 years. Each subject received a single dose (80 mg) of one of the 2 fluvastatin formulations. The tablet was orally administered with 240 ml water after at least 10 hours of fasting. 30 min. before administration of the tablets, a standard high-calorie, high-fat breakfast was served. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dosing and at 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10, 12, 16 and 24 hours after administration of the products.

*Results*

9 subjects dropped out of the study (3 subjects did not show up for period 2, another subject withdrew for personal reasons, two subjects due to adverse effects and 3 subjects due to

prohibited drug use). All were excluded from the statistical analysis. 155 subjects were eligible for pharmacokinetic analysis.

**SUMMARY OF RESULTS**
**(+)-3R,5S-FLUVASTATIN**
**N = 154**

**Pharmacokinetic Parameters**

| Parameters | | Test (Fluvastatin Sodium (A)) Mean | SD | CV (%) | Reference (Locol (B)) Mean | SD | CV (%) |
|---|---|---|---|---|---|---|---|
| $AUC_{0-t}$ | (ng·h/mL) | 223.39 | 157.31 | 70.42 | 240.12 | 147.10 | 61.26 |
| $AUC_{0-inf}$ * | (ng·h/mL) | 237.63 | 162.31 | 68.30 | 253.89 | 150.10 | 59.12 |
| $C_{max}$ | (ng/mL) | 99.63 | 110.82 | 111.24 | 89.13 | 55.39 | 62.15 |
| Residual Area* | (%) | 1.66 | 2.22 | 133.90 | 1.44 | 1.81 | 125.79 |
| $T_{max}$ | (h) | 4.71 | 1.96 | 41.73 | 4.85 | 2.25 | 46.40 |
| $T_{max}$ ** | (h) | 4.50 | 2.00 | - | 4.50 | 3.00 | - |
| $K_{el}$ * | ($h^{-1}$) | 0.4047 | 0.1619 | 40.01 | 0.4106 | 0.1663 | 40.49 |
| $T_{½ el}$ * | (h) | 2.04 | 0.96 | 47.31 | 2.09 | 1.24 | 59.14 |

* For these parameters, N = 137.
** Medians and interquartile ranges are presented.

**Fluvastatin Sodium (A) vs Locol (B)**

| | $AUC_{0-t}$ | $AUC_{0-inf}$ * | $C_{max}$ |
|---|---|---|---|
| Ratio[1] | 90.19% | 89.53% | 92.72% |
| 90 % Geometric C.I.[2] | 84.77 % to 95.96 % | 84.34 % to 95.03 % | 83.88 % to 102.49 % |
| Intra-Subject CV | 33.70 % | 30.36 % | 56.95 % |

[1] Calculated using least-squares means according to the formula: $e^{(\text{Fluvastatin Sodium (A) - Locol (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data
* For this parameter, N = 137.

*MULTIPLE DOSE, STEADY STATE, FASTING STUDY*

A multiple-dose, randomised, two-period, two-treatment, two-sequence, single-center, crossover bioequivalence study was carried out under steady-state, fasting conditions in 74 healthy male subjects, aged 22-55 years. Each subject received a single dose (80 mg) of one of the 2 fluvastatin formulations. The tablet was orally administered with 240 ml water after at least 10 hours of fasting. The volunteers fasted ≥ 2 h (day 1-4) and ≥ 4 h (day 5) after administration of the tablets. This was followed by a meal, and subjects were asked to – but not required to – consume the entire meal. In each period 1 x 80 mg was administered once daily for 5 consecutive days (a total dose of 400 mg). Subjects were confined to the CRO facility 10 hours prior to the first dose until 24h after the 5th (last) dose – in each period.

Blood samples were collected at pre-dosing on Days 1, 3, 4, and 5 and at Day 5 also at 0.50, 1.00, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10, 12, 16 and 24 hours after administration of the products.

*Results*

5 subjects dropped out of the study (one subjects did not show up for period 2, 3 subjects due to adverse effects and one subject due to prohibited drug use). All were excluded from the statistical analysis. 69 subjects were eligible for pharmacokinetic analysis.

**SUMMARY OF RESULTS**
**(+)-3R,5S-FLUVASTATIN**
**N = 69**

**Pharmacokinetic Parameters**

| Parameters | | Test (Fluvastatin Sodium (A)) Mean | SD | CV (%) | Reference (Locol (B)) Mean | SD | CV (%) |
|---|---|---|---|---|---|---|---|
| $AUC_{0-\tau\ ss}$ | (ng·h/mL) | 149.11 | 73.99 | 49.62 | 133.55 | 63.31 | 47.40 |
| $C_{max\ ss}$ | (ng/mL) | 28.40 | 13.73 | 48.35 | 28.81 | 13.15 | 45.66 |
| $C_{min\ ss}$* | (ng/mL) | 1.13 | 0.73 | 64.37 | 1.18 | 0.80 | 67.46 |
| $T_{max}$ | (h) | 3.58 | 1.56 | 43.49 | 3.38 | 2.79 | 82.62 |
| $T_{max}$** | (h) | 3.00 | 1.50 | - | 3.00 | 1.75 | - |
| Fl* | (%) | 423.55 | 132.81 | 31.36 | 482.50 | 136.96 | 28.39 |

* For these parameters, N = 26 for Treatment A and N = 37 for Treatment B.
** Medians and interquartile ranges are presented.

**Fluvastatin Sodium (A) vs Locol (B)**

| | $AUC_{0-\tau\ ss}$ | $C_{max\ ss}$ |
|---|---|---|
| Ratio[1] | 111.39% | 98.97% |
| 90 % Geometric C.I.[2] | 103.81 % to 119.53 % | 91.89 % to 106.59 % |
| Intra-Subject CV | 25.20 % | 26.56 % |

[1] Calculated using least-squares means according to the formula: $e^{(\text{Fluvastatin Sodium (A) - Locol (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data

In agreement with the EU guideline on bioequivalence of modified-release products, the 3 types of BE studies required, have been performed;
In all 3 studies, the limits 80-125% for the 90% CI are met for the relevant PK parameters.

As the (+)-enantiomer of fluvastatin is the active one, it is acceptable to have carried out the analysis on this enantiomer, even when it appears that Fluvastatin is the racemic form in this product.

By comparison of the results from the 2 single dose fasting and fed studies it can be concluded that the fluvastatin prolonged-release tablets applied for exhibit a food effect. However, the product can be taken with or without food, as the food effect is clinically not relevant (specified in the SPC).

It can be concluded that Fluvastatine Aurobindo SR 80 mg prolonged-release tablets and Lescol 80 mg prolonged-release tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The RMS has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

### IV.3 Risk Management Plan

Fluvastatin was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of fluvastatin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

## V. USER CONSULTATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Lescol marketed by Novartis Healthcare A/S.

The applicant has made a commitment to update the SPC according to a future harmonised SPC for Lescol as a consequence of an article 30 referral (in case the referral will be started).

Readability test

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The readability test has been sufficiently performed.

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

Fluvastatine Aurobindo SR 80 mg prolonged-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Lescol. Lescol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other fluvastatin containing products.

A European harmonised birth date has been allocated (1993-08-23) and subsequently the first data lock point for fluvastatin is 2009-08, after which the PSUR submission cyclus is 3 years.

The date for the first renewal was: 12 June 2013.

The following post-approval commitments have been made during the procedure:

- The enclosed stability studies will be continued.
- The first 3 commercial batches will be put on stability and tested according to the stability protocol as presented in section P.8.1.
- The applicant has made a commitment to update the SPC according to a future harmonised SPC for Lescol as a consequence of a article 30 referral (in case the referral will be started).

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| - | - | - | - | - | - |