C B G
M E B

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fluvastatine Accord 80 mg prolonged-release tablets Accord Healthcare Ltd, United Kingdom

fluvastatin (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2384/001/DC
Registration number in the Netherlands: RVG 109965

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Pharmacotherapeutic group:	HMG CoA reductase inhibitors
ATC code:	C10AA04
Route of administration:	oral
Therapeutic indication:	dyslipidaemia; secondary prevention in coronary heart disease
Prescription status:	prescription only
Date of authorisation in NL:	28 September 2012
Concerned Member States:	Decentralised procedure with AT, BG, CY, EE, FR, IE, IT, LT, LV, MT, NO, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Fluvastatine Accord 80 mg prolonged-release tablets from Accord Healthcare Ltd. The date of authorisation was on 28 September 2012 in the Netherlands.

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 interventions.

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

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. Fluvastatin exerts its main effect in the liver and is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma cholesterol concentration.
Fluvastatin reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C in patients with hypercholesterolaemia and mixed dyslipidaemia.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lescol XL 80, prolonged-release tablets (NL License RVG 25187) which has been registered in the Netherlands by Novartis Pharma B.V. since 19 June 2001 (original product). In addition, reference is made to Lescol XL authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Lescol® XL 80 mg, prolonged-release tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB 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.

Active substance
The active substance is fluvastatin sodium, an established active substance described in the United States Pharmacopoeia (USP*). The crystalline form of fluvastatin sodium is described in the European Pharmacopoeia (Ph.Eur.*). It is a white to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder, which is soluble in alcohol, methanol and water. Fluvastatin sodium amorphous is a racemic mixture.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of fluvastatin sodium amorphous consists of two steps. Sufficient information has been provided on the starting material, solvents and reagents.

Quality control of drug substance
The control tests and specifications for drug substance are adequately drawn up. The specification meets the requirements of the monograph in the Ph.Eur. and USP. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for 12 batches stored at 2-8°C (up to 60 months) and 25ºC/60% RH (up to 24 months). All long-term results were well within the specification and no significant changes have been observed.
Based on the provided stability data, the proposed retest period of 24 months can be granted for the drug substance stored between 2°C and 8°C in the tightly closed original container in order to protect from moisture and light.

** USP and Ph.Eur. are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition
Fluvastatine Accord 80 mg is a yellow colored, round, biconvex, beveled edged film coated tablet, debossed with "F80" on one side and plain on other side. The tablet contains 84.280 mg of fluvastatin sodium equivalent to 80 mg fluvastatin.

The prolonged-release tablets are packed in OPA-Al-PVC/Al blisters.

The excipients are:

Tablet core - cellulose microcrystalline, potassium hydrogen carbonate, povidone K-30, hydroxy propyl cellulose, hypromellose K 100, hypromellose K 4M , magnesium stearate.
Film-coat - polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Proposed excipients are all described in Ph.Eur. and are standard established tablet excipients. The coating mixture is controlled by in-house specification, but the components of the mixture are in line with the Ph.Eur. The drug product shows dissolution profiles in purified water, pH 1.0, pH 4.5, pH 6.0 and pH 6.8, comparable to the innovator product. Dissolution data at pH 1.0 and pH 4.5 are performed without sink conditions, but show similar behaviour.
The pharmaceutical development has been sufficiently described.

Manufacturing process
The manufacturing process consists of dry mixing by roll compaction as the drug substance is heat and moisture sensitive. As it concerns a prolonged-release tablet, the manufacturing process is considered to be non-standard. Process validation data have been presented on three batches. The validated batch size is also the proposed commercial batch size and thereby acceptable.

Control of excipients
All excipients comply with the European Pharmacopoeia except for Opadry Yellow, for which an in-house specification has been laid down. These specifications are acceptable.

Quality control of drug product
The drug product specifications cover all appropriate parameters for this dosage form. The specification includes tests for description, average weight of tablets, water content, dissolution, uniformity of dosage units, related substances, assay and microbial examination. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches as used for process validation. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
Stability data have been provided on the drug product stored at 25°C/60% RH and 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. As the drug product is packed in Alu-Alu blisters, no photostability study is deemed necessary. However, given the observed increase in impurities from a forced degradation study under photolytic stress conditions and supported by the storage condition stated in the USP monograph on Fluvastatin capsules, the product should be protected from light and moisture.
The proposed shelf-life of 24 months was granted, with the applicable storage condition 'Store below 30°C in the original container in order to protect from light and moisture'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate used in the formulation is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Lescol XL 80, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of fluvastatin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test product Fluvastatine Accord 80 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Lescol XL 80 mg prolonged-release tablets sourced from the UK market (Novartis Pharmaceuticals UK Ltd). The studies were a single dose fasted study, a single dose fed study and a multiple dose fasted study.

According to the guideline, for the application of a prolonged-release formulation bioequivalence studies should be performed in a single dose and in steady state conditions. Furthermore the effect of food should be investigated in a single dose study after a high fat meal. The number and type of bioequivalence studies reported are sufficient for this application.
Bioequivalence is to be established based on data of active enantiomer (+)-(3R,5S)-fluvastatin in accordance with current guidelines.

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – single-dose, fasted conditions

Design
A single-dose, randomised, two treatment, four-period, two sequence, replicate, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 19-41 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 an overnight fast of at least 10 hours. There were 4 dosing periods, separated by a washout period of 8 days.
Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.25, 4.5, 4.75, 5.0, 5.5. 6.0, 6.5, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

This design is acceptable, since a wash-out period of 8 days is long enough, the sampling period is long enough and the sampling scheme adequate.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for chiral analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn from the study at check-in of the 3rd period due to a positive urine drug scan. Another subject withdrew at check-in of the 4th period by his own choice. All subject data was included in the pharmacokinetic analysis, including the completed periods of the two drop-outs. This is according to protocol, drop-out subject data is included if at least two periods have been completed. Therefore all 30 subjects were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of (+)-(3R,5S)-fluvastatin under fasted conditions.

Treatment N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h

Test	151.0 ± 83.5	165.1 ± 92.9	41.0 ± 19.4	3.00 (1.00-4.75)	4.4 ± 3.5
Reference	146.1 ± 73.3	159.4 ± 76.0	37.7 ± 21.0	2.75 (1.00-6.00	5.2 ± 7.9
***Ratio (90% CI)**	0.91-1.10	0.90-1.11	1.00-1.24	--	--
CV (%)	27.5	27.9	36.3	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of fluvastatin under fasted conditions, it can be concluded that Fluvastatine Accord 80 mg and Lescol XL 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.

A number of 2 unrelated adverse events were reported, 1 subject reported nausea and diarrhoea after dosing in period 2 (reference product) and for 1 subject increased white blood cell count was reported post study (after test product).

Bioequivalence study II – single-dose, fed conditions

Design
A single-dose, open label, randomised, two-treatment, four-period, two sequence, replicate, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 21-38 years. On dosing days, after an overnight fasting period of at least 10 hours, the subjects consumed a vegetarian breakfast before dosing. This consisted of one toast with butter, a chickpea snack, two vegetable cutlets and a glass of milk. This high-fat/ high-calorie meal constituted of carbohydrates (± 260 Kcal), fats (± 540 Kcal) and proteins (± 137 Kcal). The subjects received the formulation 30 minutes after the meal was served. The meal was completely consumed and the dose was administered with 240 ml water. There were 4 dosing periods, separated by a washout period of 7 days.
Blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.5, 8.0, 8.5, 9.0, 10, 12, 16, 18, 24 and 36 hours after administration of the products.

The design is acceptable for this bioequivalence study. The wash-out and sampling period are long enough and the sampling scheme is adequate regarding the expected pharmacokinetic parameters.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. Widening of the acceptance criteria for the 90% confidence interval of the C_{max} is adequately justified as the intra subject CV of ln-transformed C_{max} of the reference product was ≥ 30%. Therefore, the methods used in this study for the pharmacokinetic calculations and the formula calculation for the widened 90% confidence interval for the C_{max} for the statistical evaluation are considered acceptable.

Results
In total, there were 4 drop-outs. One subject was discontinued on dosing day 1 of the study due to emesis, another was discontinued due to a positive alcohol breath test before dosing in period 2. A third

subject did not show up for check-in of period 2 and another subject was discontinued due to emesis on the first day of the second period. Data for a total of 26 subjects was included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of (+)-(3R,5S)-fluvastatin under fed conditions.

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	344.6 ± 144.5	357.4 ± 143.8	110.0 ± 48.3	5.5 (2.00-18.00)	3.3 ± 5.4
Reference	329.1 ± 141.9	338.9 ± 142.2	112.7 ± 68.3	5.75 (2.00-18.00)	2.9 ± 3.2
***Ratio (90% CI)**	0.96-1.16	0.99-1.16	0.92-1.27	--	--
CV (%)	24.4	25.2	55.3	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and $AUC_{0-\infty}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of fluvastatin under fed conditions, it can be concluded that Fluvastatine Accord 80 mg and Lescol XL 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.

A total of 4 adverse events were reported, by 2 subjects. For the first subject vomiting, headache and nausea was reported, after dosing of the test product in period 1. The relationship was given as unlikely. The second subject experienced vomiting after the test product in period 2. The relationship to the study drug was reported as possible.

Bioequivalence study III – multiple-dose, fasted conditions

Design
A multiple-dose, randomised, two-period, two-treatment crossover steady-state bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, with a mean age of 28.2 ± 6.8 year. During each period, the subjects were administered one tablet daily, for 7 days in a row and each tablet was taken after an overnight fast and with 240 ml drinking water. There were 2 dosing periods, separated by a washout period of 8 days.
Blood samples were collected prior to each dose and over a 48 hour period following dose 7, at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36 and 48 hours post dose.

The design is acceptable for this bioequivalence study. The wash-out period is long enough, as well as the sampling period and the sampling scheme is adequate to estimate pharmacokinetic parameters.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
During the first period, two drop-outs did occur; 1 on his own accord and 1 due to emesis. During the second period, a total of 4 subjects discontinued the study on their own accord and 2 subjects were discontinued on medical grounds. Only samples and data for the 52 subjects who completed the study were included in pharmacokinetic and statistical analysis.

Table 3. Pharmacokinetic parameters of (+)-(3R,5S)-fluvastatin in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=52	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	167.8 ± 75.5	39.8 ± 20.1	0.3 ± 0.8	582.0 ± 185.6
Reference	163.0 ± 78.2	41.0 ± 21.3	0.3 ± 0.6	616.7 ± 229.3
***Ratio (90% CI)**	0.95-1.10	0.89-1.08	--	0.88-1.04
CV (%)	23.3	30.2	--	26.3

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

The 90% confidence intervals calculated for AUC_τ, C_{max} and PTF are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. In this case C_{min} is not usable as a parameter as $C_{min,ss}$ is in most cases zero for both the test and reference formulation and it is agreed that PTF is used as a bioequivalence standard, as predefined in the protocol. Based on the pharmacokinetic parameters of fluvastatin at steady state, it can be concluded that Fluvastatine Accord 80 mg and Lescol XL 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.

A total of 12 adverse events were reported by 8 subjects. During the study period of the test product a total of 3 adverse events were reported to be significant and 5 to be mild. All significant adverse events were possibly related to the test study drug; 1 subject reported diarrhoea and abdominal pain and 1 subject was reported to experience only diarrhoea. The 5 mild adverse events which were reported during the test product study period; increased blood creatine phosphokinase, diarrhoea and abdominal pain in 1 subject and only diarrhoea in 1 subject possibly related to the study drug and pyrexia in 1 subject, not related to the study drug. During the study period of the reference product, 4 possibly related, mild adverse events were reported in 4 subjects; increased blood creatine phosphokinase, abdominal pain, upper abdominal pain and vomiting.

The MEB has been assured that the three bioequivalence studies have 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).

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 post authorisation which are not adequately covered by the current SmPC. 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. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lescol XL.

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 2 participants, followed by two rounds with 10 participants each.
There were 15 questions addressing the key safety messages and presentation of information. The questions cover the areas, locate information in the package leaflet, understand it and know how to act on it. Four questions were asked which provide overall feedback regarding the leaflet. 15 participants (68% ranked the leaflet as very easy or easy to read. Positive is that the leaflet is clearly written, with clear headings and good bullet points. Negative is that there is a lot of information.
In the first round all questions were answered correctly, but for some questions the difficulty in locating and understanding was basic, especially question 1 caused problems. But as all questions were answered correctly, no modifications were done between in first and second round. In the second round again all questions were answered correctly. In this round there were no questions which caused problems.
In total 100% of the participants were able to find the correct information in the package leaflet and the overall percentage of correct answers was 100%. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fluvastatine Accord 80 mg prolonged-release tablet have a proven chemical-pharmaceutical quality and is a generic form of Lescol XL 80. Lescol XL 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 is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fluvastatine Accord 80 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 June 2012. Fluvastatine Accord 80 mg prolonged-release tablets was authorised in the Netherlands on 28 September 2012.

The date for the first renewal will be: 1 August 2016.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location.	NL/H/2384/ 001/IA/G/ 001	IA/G	24-12-2013	23-1-2014	Approval	N
Update of sections 4.4. 4.6 and 4.8 of the SmPC and sections 2, 4 and 6 of PL for Fluvastatine Accord 80 mg, in order to make these in line with the reference product of Novartis Pharmaceuticals UK.	NL/H/2384/ 001/IB/002	IB	28-11-2013	14-2-2014	Approval	N
Addition of a batch control/testing site.	NL/H/2384/ 001/IA/G/ 003	IA/G	24-4-2014	28-5-2014	Approval	N
Minor change to the restricted part of an Active Substance Master File.	NL/H/2384/ 001/IB/G/ 004	IB/G	8-8-2014	7-9-2014	Approval	N