CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Pravastatinenatrium 10 mg, 20 mg and 40 mg TEVA, tablets
Teva Nederland B.V., the Netherlands

pravastatin (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/1931/001-003/DC
Registration number in the Netherlands: RVG 106528-106530

6 June 2011

Pharmacotherapeutic group:	lipid modifying agents - HMG-CoA reductase inhibitors
ATC code:	C10AA03
Route of administration:	oral
Therapeutic indication:	treatment of primary hypercholesterolemia or mixed dyslipidaemia; reduction of cardiovascular mortality and morbidity; reduction of post transplantation hyperlipidaemia in patients receiving immunossupressive therapy following solid organ transplantation
Prescription status:	prescription only
Date of authorisation in NL:	30 May 2011
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, PT
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 (SPC), 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 Pravastatinenatrium 10 mg, 20 mg and 40 mg TEVA, tablets from Teva Nederland B.V. The date of authorisation was on 30 May 2011 in the Netherlands.

The product is indicated for:

- *Hypercholesterolaemia*
  Treatment of primary hypercholesterolemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.
- *Primary prevention*
  Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia and at high risk of a first cardiovascular event, as an adjunct to diet.
- *Secondary prevention*
  Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors.
- *Post transplantation*
  Reduction of post transplantation hyperlipidaemia in patients receiving immunossupressive therapy following solid organ transplantation.

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

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis, and produces its lipid-lowering effect in two ways. Firstly, with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL-cholesterol. Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL cholesterol, the LDL-cholesterol precursor.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Selektine 10, 20 and 40 mg tablets (NL License RVG 13755, 13756 and 20665). The 10 and 20 mg strengths have been registered through MRP (FR/H/252/01-3) in the Netherlands since 1990, and the 40 mg strength has been registered since 1996 by Bristol-Myers Squibb B.V. In addition, reference is made to Selektine authorisations in the individual member states. For Portugal reference is made to the European reference medicinal product Selektine 10 mg registered in the Netherlands, as this strength has not been registered in Portugal.

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 a bioequivalence study in which the pharmacokinetic profile of the 40 mg product is compared with the pharmacokinetic profile of the reference product Lipostat 40 mg 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. These generic products can be used instead of their 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 medicinal product.

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 these product types 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 pravastatin sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Pravastatin sodium is a white to yellowish white powder or crystalline powder, freely soluble in water and methanol, and soluble in anhydrous ethanol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and its additional requirements from the CEP. The MAH has added a test and limit for residual solvents, microbiological test and particle size distribution. The methods have been described and validated. The specification is sufficiently justified. Sufficient batch analysis data have been provided.

Stability of drug substance
Stability data have been provided for drug substance is stored at 5°C (long term) for 6 to 36 months and at 25°C/60%RH for a period of 6 months. These conditions are in line with the guideline on stability testing when the active substance is intended for storage in a refrigerator. Based on the results, a retest period of 24 months could be granted when stored at 2-8°C in the approved package.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Pravastatinenatrium 10 mg TEVA is a pink, round, shallow convex tablet, with the inscription "93" on one side and "771" on the other.
Pravastatinenatrium 20 mg TEVA is a light yellow, round, shallow convex tablet, with the inscription "93" on one side and "7201" on the other.
Pravastatinenatrium 40 mg TEVA is a light green, round, shallow convex tablet, with the inscription "93" on one side and "7202" on the other.

The tablets are packed in transparent PVC-PE-PVdC/Alu blisters.

The excipients are: lactose anhydrous, povidone (PVP K-30), crospovidone, anhydrous calcium hydrogen phosphate (E341), sodium stearyl fumarate, cellulose microcrystalline (E460), croscarmellose sodium (E466) and red iron oxide (E172) (10 mg), yellow iron oxide (E172) (20 mg); quinoline yellow (E104) and brilliant blue FCF (E133) (40 mg).

The tablet compositions are dose proportional.

Pharmaceutical development
The development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of tablet formulations and most are also present in the innovator product. The packaging materials are usual and suitable for the product at issue.
Dissolution studies were performed to compare the developed tablets with the reference products and with other authorized products. The biobatches of 40 mg tablets (test and reference) showed very similar dissolution behaviour, over 80% was dissolved in 10 minutes. Four batches of the test tablets (10, 20, 40, 40 mg) showed within-strength and between strength good dissolution profile consistency.
The pharmaceutical development has been adequately performed and sufficiently described.

Manufacturing process
The tablets are prepared by sieving, mixing, blending and tabletting steps. The tablet compositions are proportional, the colorants differ. The applied direct compression tabletting is considered a standard production process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three consecutive production batches per strength.

Control of excipients
The excipients comply with the Ph.Eur, or an in-house specification. Compliance to directive 65/45/EC was stated for the colorants. These specifications are acceptable.

Quality control of drug product
The product specification for the tablets is in line with general Ph.Eur. requirements and ICH guidelines. The product specification includes tests for description, appearance, identification (HPLC, UV and sodium), dissolution, uniformity of mass, assay, related substances, microbiological purity, and identification of colourants The specification also includes average weight, individual weight, thickness, hardness, and friability, they are performed as in-process controls. The end of shelf-life limits for the related substances are slightly higher than the release limit. The analytical methods have been adequately described and validated. Batch analyses results have been provided on two pilot-scale batches of the 10 mg and 40 mg product and one batch of the 20 mg product; all results comply with the proposed specification.

Stability of drug product
Pilot-scale batches as well as production-scale batches have been included in the stability studies The tablets have been stored at 25°C/60%RH (up to 24 months), 30°C/60% RH (12 months) and 40°C/75% RH (6 months) in PVC-PE-PVdC/aluminium blisters. The product is not stable at 40°C/75%RH. At the other storage conditions an increase in one impurity was noted. A decrease in assay was noted as well. All results remained with in the limits. The approved shelf-life is 24 months when stored below 30°C in the original packaging in order to protect from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The lactose anhydrous is derived from milk and calf rennet. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption.

II.2 Non-clinical aspects

These products are generic formulations of Selektine 10, 20 and 40 mg, 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 pravastatin 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Pravastatinenatrium 40 mg TEVA tablets (Teva Nederland B.V., NL) is compared with the pharmacokinetic profile of the reference product Lipostat 40 mg tablets (Bristol-Myers Squibb Pharmaceuticals, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study 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.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-55 years. Each subject received a single dose (40 mg) of one of the 2 pravastatin sodium formulations. The tablet was orally administered with 240 ml water after a 10 hour fasting period, which was continued until 4 hours after administration..There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is 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
Fifty-eight subjects completed both study periods and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pravastatin under fasted conditions.

Treatment N=58	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	118.00 ± 63.2	119.38 ± 63.3	50.08 ± 31.6	1.0 (0.75 – 3)	2.52 ± 0.8
Reference	124.14 ± 71.3	125.44 ± 71.1	53.67 ± 39.7	1.0 (0.5 – 1.75)	2.68 ± 0.9
***Ratio (90% CI)**	0.96 (0.88-1.04)	0.96 (0.89-1.04)	0.96 (0.86-1.07)	--	--

CV (%)	27.4	26.3	36.1	--	--

$AUC_{0-\infty}$ 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 pravastatin under fasted conditions, it can be concluded that Pravastatinenatrium 40 mg TEVA and Lipostat 40 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Pravastatin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of pravastatin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to different strengths
The 10 and 20 mg tablets are dose proportional with the 40 mg tablet. The results of the bioequivalence study performed with the 40 mg tablet therefore apply to the other tablets.

The MEB 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).

Risk management plan
Pravastatin was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of pravastatin 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 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. 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

SPC
The SPC of pravastatin sodium was harmonized during an Art. 30 referral procedure (EU Decision on 2 March 2004). Thereafter changes in the SPC were approved as result of the determination of the Core Safety Profile in August 2008 and other text proposals as recommended by the PhVWP in 2002 and 2007. All these changes are incorporated in the SPC.

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.
Questions were designed to determine whether users can identify key information that is necessary for appropriate use. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 20 questions related to the

content of the PIL. Three questions were related to the structure/layout of the PIL. Respondents were asked to give their answer in their own words.
In round 1, on average 99.5% of the time the correct section was located to answer the question. Each question was correctly answered 100% of the time. For some questions difficulties were observed in location the correct section. Therefore, the text ‘Statins such as Pravastatin may sometimes cause lung disease, especially when they are used over a long period of time’ was emboldened to improve the ability of users to locate this information. In the second round 99.5% of the participants were able to locate the section and 100% were able to answer the questions. Therefore no further changes were considered to be required. The user test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pravastatinenatrium 10 mg, 20 mg and 40 mg TEVA, tablets have a proven chemical-pharmaceutical quality and are generic forms of Selektine 10, 20 and 40 mg tablets. Selektine 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 SPC, package leaflet and labelling are in the agreed templates and are in agreement with other pravastatin containing products.

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 Pravastatinenatrium 10 mg, 20 mg and 40 mg TEVA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 November 2010. Pravastatinenatrium 10 mg, 20 mg and 40 mg TEVA, tablets were authorised in the Netherlands on 30 May 2011.

A European harmonised birth date has been allocated (31 March 1989) and subsequently the first data lock point for pravastatin is March 2011. The first PSUR will cover the period from November 2010 to March 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 November 2014.

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
SPC	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