

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Pravastatine Na Stada 10 mg, film-coated tablets
Pravastatine Na Stada 20 mg, film-coated tablets
Pravastatine Na Stada 40 mg, film-coated tablets**

Stada Arzneimittel AG, Germany

pravastatin sodium

This assessment report is published by the MEB following 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/961/01-03/MR
Registration number in the Netherlands: RVG 31602, 31603, 31604**

22 January 2010

Pharmacotherapeutic group:	Serum lipid reducing agents, cholesterol and tricycleride reducers, 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 immunosuppressive therapy following solid organ transplantation.
Prescription status:	prescription only
Date of authorisation in NL:	10 September 2004
Concerned Member States:	Mutual recognition procedure DE and IT (only 20 and 40 mg)
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 Pravastatine Na Stada 10 mg film-coated tablets, Pravastatine Na Stada 20 mg film-coated tablets and Pravastatine Na Stada 40 mg film-coated tablets, from Stada Arzneimittel AG, Germany. The first date of authorisation was on 10 September 2004 in the Netherlands.

The product is indicated for:

- 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.
- 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.
- 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.
- Reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive 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 application concerns a generic application claiming essential similarity with the innovator products Selektine® 10, 20 and 40 mg tablets (NL License RVG 13755, 13756 and 20665). The 10 and 20 mg strengths have been registered in the Netherlands since 1990, whereas 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 (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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Pravasin Protect 40 mg, registered in Germany. Pravasin Protect is the trade name for the innovator product in Germany, which is identical with the innovator product on the Dutch market. 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.

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 and excipients

The active substance is pravastatin sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). 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. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur., with in-house specifications for residual solvents, determination of impurities and determination of assay. There are two manufacturers of the active substance: for one of these the CEP procedure is used, and for the other manufacturer the EDMF procedure. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches for one manufacturer.

The Active Substance Master File (ASMF) procedure is used by one manufacturer 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. After authorisation the ASMF procedure was replaced by a Certificate of the European Pharmacopoeia (CEP) (see table Steps taken after finalisation of the initial procedure at Page 9).

The CEP procedure is used by the second manufacturer 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, and 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 Ph.Eur. After authorisation an updated CEP was submitted (see table Steps taken after finalisation of the initial procedure at Page 9).

For one manufacturer, stability data were provided for 11 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 months. Based on the data submitted, a retest period was granted of 36 months when stored at 2-8°C in the original package. For the other manufacturer no retest period was granted. Therefore, the active substance should be tested immediately prior to use.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for colorants iron oxide red and iron oxide yellow for which reference is made to the French pharmacopoeia.

Medicinal Product

Composition

Pravastatine Na Stada 10 mg film-coated tablets contain as active substance 10 mg of pravastatin sodium and are pink-peach indented capsule shape tablets with "10" on one side.

Pravastatine Na Stada 20 mg film-coated tablets contain as active substance 20 mg of pravastatin sodium and are yellow indented capsule shape tablets with "20" on one side.

Pravastatine Na Stada 40 mg film-coated tablets contain as active substance 40 mg of pravastatin sodium and are yellow indented capsule shape tablets with "40" on one side.

The tablets are packed in PVC/PCTFE-aluminium blisters.

The excipients are:

tablet core: microcrystalline cellulose (E460), croscarmellose sodium (E468), polyethylene glycol 8000, copovidone, calcium phosphate anhydrous (E341), lactose monohydrate, magnesium stearate (E470b), colloidal silicon dioxide (E551).

10 mg tablet: iron oxide red (E172), 20 and 40 mg tablets: iron oxide yellow (E172)

tablet coat: opdradry clear YS-5-7044 containing: hyprollose (E463), macrogol 400, macrogol 3350, hypromellose (E464).

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Selektine 10, 20 and 40 mg tablets.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches of each strength. For all three strengths 2 batches are on pilot scale size and 1 is on laboratory scale size.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, content uniformity, disintegration, hardness, disintegration, dissolution, degradation products, residual solvents, assay and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 4 batches of each strength of the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product

Stability data on the product have been provided for 4 batches of the 10 and 20 mg strengths in accordance with applicable European guidelines demonstrating the stability of the product over 18 months. Stability data on the product have been provided for 4 batches of the 40 mg strength in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. The labelled storage conditions are: *"Do not store above 25°C. Store in original package."*

The MAH committed to include the first three production scale batches of each tablet strength in the stability program. Results will be submitted in 6 month intervals. The MAH committed to submit updated long-term and accelerated stability data of finished product manufactured with active substance from one of the manufacturers.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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

The content of the SPC approved during the mutual recognition procedure is in accordance with the SPC harmonised via art 30 of the Directive 2001/83/EC procedure decided on by the European Commission on 2 March 2004 (EMEA/CPMP/6214/03/Final).

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Pravastatine Na Stada 40 mg is compared with the pharmacokinetic profile of the German reference product Pravasin® Protect 40 mg. Both products contain 40 mg pravastatin sodium.

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.

A randomised, single-dose, 2-way cross-over, single centre, balanced bioequivalence study was carried out under fasted conditions in 36 healthy subjects (18 males, 18 females) aged 19-53 years. For each subject there were 2 dosing periods of one of the 40 mg pravastatin formulations, separated by a washout period of at least 3 days. The tablet was orally administered with 240 ml water after 10 of hours fasting. Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis. The bioavailability of the test product Pravastatine Na Stada 40 mg tablets was compared to the German reference product Pravasin Protect 40 mg tablets, Bristol–Myers–Squibb GmbH.

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

Treatment N=36	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	169 \pm 72	173 \pm 75	79 \pm 44	0.77 (0.53–1.50)	6.9 \pm 6.1
Reference	161 \pm 77	164 \pm 78	79 \pm 44	1.0 (0.75–1.75)	5.4 \pm 3.7
Ratio (90% CI)	1.07 (0.99-1.17)	1.08 (0.99-1.18)	1.02 (0.90-1.15)	--	--
CV (%)	20.73	21.18	31.99	--	--
AUC_{0-∞} 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					

Scientific literature shows no influence of concomitant food intake on the absorption of pravastatin. Therefore, a food interaction study was not deemed necessary. 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 Pravastatine Na Stada 40 mg tablet and the German reference product Pravasin Protect 40 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The Pravastatine Na Stada 10, 20 and 40 mg tablets are dose proportional. The pharmacokinetics of pravastatin is linear in the range 10-40 mg. The results of the bioequivalence study performed with the 10 mg tablet therefore apply to the other tablet's strength.

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 sodium 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 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. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pravastatine Na Stada 10, 20 and 40 mg 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 content of the SPC approved during the mutual recognition procedure is in accordance with the SPC harmonised via art 30 of the Directive 2001/83/EC procedure decided on by the European Commission on 2 March 2004 (EMEA/CPMP/6214/03/Final).

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 agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Pravastatine Na Stada 10, 20 and 40 mg was authorised in the Netherlands on 10 September 2004. The member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Pravastatine Na Stada with the reference product, and have therefore granted a marketing authorisation.

The member states mutually recognised the Dutch evaluation of the marketing authorisation. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The first PSUR will cover the period starting from 17 May 2004 till 31 March 2008 to coincide with the renewal. Hereafter, the PSURs will be submitted three-yearly.

The date for the early renewal will be: 31 March 2009.

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

Quality – Medicinal product

- The MAH committed to investigate the difference in behaviour of the 10 mg and 20 mg tablets versus the 40 mg tablets in the stability study.
- The MAH committed to include the first three production scale batches of each tablet strength in the stability program. Results will be submitted in 6 month intervals.
- The MAH committed to submit updated long-term and accelerated stability data of finished product manufactured with active substance from one of the manufacturers.

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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	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
Change of pack size of the finished product.	NL/H/961/01-02/IA/001	IA	13-03-2007	27-03-2007	Y	N
Change of pack size of the finished product.	NL/H/961/03/IA/002	IA				
Addition of a manufacturing site responsible for primary and secondary packaging of the finished product.	NL/H/961/01-03/IA/003	IA	02-11-2007	16-11-2007	Y	N
Submission of a new or updated version of the Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance.	NL/H/961/01-03/IA/004-005	IA	17-01-2008	31-01-2008	Y	N
Change in the name of a manufacturer of the finished product.	NL/H/961/01-03/IA/006	IA	03-06-2008	17-06-2008	Y	N
Renewal of the Marketing Authorisation.	NL/H/961/01-03/R/001	Renewal	05-08-2008	07-01-2009	Y	Y, Annex I
Change to comply with an update of the relevant monograph of the Ph. Eur. The finished product manufacturer's specification for the active substance is adjusted	NL/H/961/01-03/IA/007	IA	12-08-2009	26-08-2009	Y	N
Change in pack size of the finished product within the range of the currently approved pack sizes	NL/H/961/01-03/IA/008	IA	09-09-2009	23-09-2009	Y	N

Annex I - Renewal Marketing Authorisation

Introduction

The product contains pravastatin sodium, a lipid-lowering agent which acts through the inhibition of HMG-CoA-reductase.

The product is indicated for:

- 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.
- 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.
- 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.
- Reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive therapy following solid organ transplantation.

The MAH has submitted a renewal application through the Mutual Recognition Procedure with RMS=NL. The MAH submitted several documents including the following:

- A joint PSUR for pravastatin (including data from 9 MAH's) covering the period 17 May 2004 to 31 March 2008, dated 13 April 2008.
- A Clinical Expert Statement dated 20 May 2008.
- A SPC proposal in which warnings and undesirable effects have been added that reflect the PhVWP recommendations of their December 2007 meeting.

PSUR Data Review

RMS' comment:

Pravastatin takes part in the PSUR synchronisation project of the Head of Medicines Agencies. Currently, pravastatin PSURs are being assessed by the p-RMS. Apart from the MEB's conclusions in this PSUR assessment report, the MAH should act upon the conclusions drawn in the final p-RMS PSUR assessment report.

Furthermore, as part of the PSUR synchronisation project, a Core Safety Profile (CSP) will be decided on. Once the final p-RMS assessment report has been circulated and the CSP has been agreed, the MAH should compare the agreed CSP with the currently approved SPC(s) and submit variations as required. The variations should be submitted within 60 days of receiving the final p-RMS assessment report and agreed CSP. The final assessment report and agreed CSP can be used as supporting data for these applications.

Response MAH:

We have taken notice of the above. We are prepared to act upon the conclusions drawn in the final p-RMS PSUR assessment report.

RMS' comment:

The member states agree.

World wide marketing authorisation status

The pravastatin products covered by this PSUR have gained marketing authorization in 9 countries and are marketed in 6 countries. In a MRP the Netherlands acted as Reference Member State.

Actions taken for safety reasons

During the review period no actions have been taken.

RMS' comment:

The MAH submitted a SPC proposal in which warnings and undesirable effects have been added that reflect the PhVWP recommendations of their December 2007 meeting.

Changes to the Reference safety information

The SPC was used as Reference Safety Information (RSI). During the period covered by this report, no changes to the RSI have been made.

Patient exposure

There have been no company-sponsored clinical trials running during the reporting period.

Adverse reactions

Six serious case reports with 12 serious adverse events (Arrhythmia*, Arthralgia, dizziness, Dyspnoea*, Erectile dysfunction*, Headache, Influenza like illness*, Interstitial lung disease*, Malaise*, Muscle spasms, Nausea, Thrombocytopenia*; *=unlisted) have been received. Furthermore 30 non-serious cases reporting 43 adverse events have been received.

RMS' comment:

It should be noted that in September 2007, the Pharmacovigilance Working Party considered the Overall Assessment Report for the class review of potential signals related to the use of HMG CoA reductase inhibitors. Sexual disturbance and interstitial pneumopathy were two of the potential signals. In July 2008 PhVWP agreed to change section 4.8 and 4.4 of the SPCs for HMG CoA Reductase Inhibitors with the following wording:

Section 4.4 – Special warnings and precautions for use

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Section 4.8 – Undesirable effects

The following adverse events have been reported with some statins:

- *Sleep disturbances, including insomnia and nightmares [where this is not already listed]*
- *Memory loss*
- *Sexual dysfunction [where this is not already listed]*
- *Depression*
- *Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)*

The implementation plan for the MAH's will be discussed during the September 2008 PhVWP. The MAH submitted a SPC proposal in which warnings and undesirable effects have been added that reflect the PhVWP recommendations of their December 2007 meeting.

Thrombocytopenia and dyspnoea are listed in the preliminary Core Safety Profile that will be finalised soon.

From literature, 18 articles referring to individual case safety reports were identified of which seven contain new or relevant safety information:

- Eight patients developed decreased libido during treatment with HMG-CoA reductase inhibitors for hypercholesterolemia. Two patients received pravastatin. Sexual dysfunction is listed in the reference safety information of pravastatin; decreased libido is not explicitly mentioned. A search in PubMed did not reveal any other publication concerning pravastatin and libido. No safety concern was elicited from these case reports.
- A 55-year-old man with myasthenia gravis, hyperlipidaemia and hypertension developed exacerbations of myasthenia gravis during treatment with atorvastatin, lovastatin, pravastatin and simvastatin. Myasthenia gravis or aggravation of this condition is not listed as undesirable effect of pravastatin. A search in PubMed identified only one additional publication concerning statins and myasthenia where an unspecified statin appeared to have exacerbated underlying myasthenic weakness whereas in 3 additional cases *de novo* antibody formation appeared to be the most likely explanation of the reported symptoms of myasthenia gravis. No firm conclusion was elicited from this case report.
- Seven patients developed interstitial lung disease during treatment with atorvastatin, pravastatin or simvastatin, and two patients subsequently died. Two patients received pravastatin, one of them died. Progressive dyspnea is not listed in the reference safety information of pravastatin. In either case the patients had risk factors for developing lung diseases and symptoms did not improve after discontinuation of pravastatin. A causative mechanism remains unclear. No safety concern was elicited from these case reports.
- A 60-year-old man developed bilateral pleural effusions while receiving pravastatin. Pleural effusion is not listed in the reference safety information of pravastatin. Course of events and improvement after cessation of pravastatin suggest a causal relationship. A search in PubMed for statins and pleural effusion revealed only one additional case report with simvastatin. No safety concern was elicited from this case report.
- An 82-year-old woman developed Ro/SSa-positive subacute cutaneous lupus erythematosus during treatment with simvastatin; she developed a recurrence of her rash during subsequent treatment with pravastatin. Cutaneous lupus erythematosus is not listed in the reference safety information of pravastatin. Recurrence of her rash on each reintroduction within a few days after re-administration of simvastatin as well as pravastatin suggests a causal relationship of either statin. No safety concern was elicited from this case report.
- A 65-year-old woman developed muscular disorders during concomitant treatment with colchicine for gout and pravastatin. Interactions between colchicine and statins (simvastatin, fluvastatin) have been described. Since many statins are metabolised by CYP3A4, as is colchicine, this has been proposed as one possible mechanism. However, fluvastatin and pravastatin are cleared through different isoenzymes. Myopathy is a known side effect of colchicine as well as for pravastatin. In this case a drug interaction is merely a theoretical assumption since both drugs were discontinued and the re-exposition of colchicine was done at a dose a third lower than the initial dose. Therefore, absence of symptoms after re-administration of colchicine may also be explained by the lower dose. No safety concern was elicited from this case report.
- A 62-year-old man developed rhabdomyolysis while receiving pravastatin and concomitant efalizumab. Rhabdomyolysis is a known side effect of statins and adequately listed in the reference safety information of pravastatin. In this case the cause for rhabdomyolysis remains unclear since symptoms improved before treatment with pravastatin and efalizumab was stopped. A drug-drug interaction is only hypothetically, the clinical course does not support this hypothesis. No safety concern was elicited from this case report.

RMS' comment:

- *Interstitial lung disease has been added to section 4.4 of the SPC proposal.*
- *The MAH should monitor unlisted interaction cases including colchicine and efalizumab.*

Cases with fatal outcome

None of the cases reported to the MAH resulted in death. A 78-year-old male patient reported by Walker et al. died 18 months after onset of suspected interstitial lung disease. The MAH considers there is no indication that the death is to be considered as outcome of the event.

Studies

No newly analysed studies became available during the period under review. No new safety studies are currently being planned, have been initiated or are being performed for the product.

A search for relevant safety studies with pravastatin published in the literature was performed, with the following results:

- *Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA: the Journal of the American Medical Association 292: 2585-2590, No. 21, 1 Dec 2004 - USA.* The combined use of statins and fibrates increased the risk of hospitalisation with rhabdomyolysis compared with statin monotherapy. Rhabdomyolysis is a known side effect of statins. The results of this study confirm that the risk for this side effect is higher with cerivastatin and fibrates. Pravastatin, atorvastatin and simvastatin have a markedly lower risk for developing rhabdomyolysis.
- *Velo GP, Magro L, Cocci A, Dusi G, Ros B, Salvo F, Leone R. Statins and hepatic reactions: data from spontaneous reporting in Italy. Drug Safety 28: 960-961 (plus poster), No. 10, 2005 - Italy.* Fluvastatin use appears to be associated with a higher risk of hepatic adverse drug reactions (ADRs) than use of other statins, according to results from a study presented at the 5th Annual Meeting of the International Society of Pharmacovigilance held in Manila, Philippines in October 2005.
- *Conforti A, Magro L, Moretti U, Scotto S, Motola D, Salvo F, Ros B, Leone R. Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. Drug Safety 29: 1163-1172, No. 12, 2006.* Liver disorders appear to be more frequent and serious with fluvastatin than with other statins. Hepatic side effects including hepatitis and fulminant hepatic necrosis are known to occur with pravastatin. The publications confirmed that the (reporting) incidence of hepatic side effects with pravastatin is comparable to those with simvastatin and atorvastatin.
- *de Langen JJ, van Puijenbroek EP. HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre. Netherlands Journal of Medicine 64: 334-338, No. 9, Oct 2006.* The long-term use of statins appears to be associated with an increased risk of neuropathy, according to the researchers. Peripheral polyneuropathy, in particular if used for a long period of time, is a known side effect of pravastatin.
- *Three articles regarding cancer: (1) Bonovas S, Sitaras NM. Does pravastatin promote cancer in elderly patients? A meta-analysis. CMAJ: Canadian Medical Association Journal 176: 649-654, No. 5, 27 Feb 2007, (2) Brophy JM. Pravastatin and cancer: an unproven association. CMAJ: Canadian Medical Association Journal 176: 646-647, No. 5, 27 Feb 2007, (3) Tayler ML, Wells BJ, Smolak MJ. Statins and cancer: a meta-analysis of case-control studies. Eur J Cancer Prev. 2008 Jun;17(3):259-68.* According to Greek researchers, the use of pravastatin may be associated with an increased risk of cancer in elderly patients. Increased risk of cancer is not a known effect of statins. A meta-analysis of case control studies found a significant association between statin usage and any cancer, but when stratified by cancer type, only the association with colon cancer remained. Overall, the MAH considers there is no evidence that statin use may be associated with an increased risk of cancer.

RMS' comment:

- No new safety issues have been identified from published studies.
- In November 2002 the results of PROSPER study (Shepherd et al.) were published in the Lancet where a significantly higher incidence of new cancer diagnoses was observed in patients on pravastatin in comparison with those on placebo. This potential safety signal has stimulated the review of statins and risk of cancer. The PhVWP has concluded that the assessment of available data on statins and cancer occurrence does not change the positive benefit-risk profile of a statin. The available clinical data are reassuring and provide no evidence for an increased risk of cancer in the general patient population treated with a statin for up to 5 years, although no conclusive data are available concerning effect of statins on cancer risk in the elderly (≥ 70 years). The long-term data on cancer risk of statins are still limited.
- Cancers should continue to be monitored in upcoming PSURs and in ongoing clinical trials if applicable.

Other information

Lack of efficacy

No unusual lack of efficacy, which might represent a significant hazard to the treated population, was reported.

Late breaking information

The MAH states that at the DLP date, there was no important, new information was received.

Drug interactions, Overdose, Drug abuse or misuse, Medication errors, Special patient groups, Pregnancy and lactation, Effects of long term treatment

During the period covered by this report, there has been no new information on the above mentioned topics.

Overall conclusions of the MAH

There were neither changes in characteristics nor in frequency of listed reactions. Serious unlisted reactions were considered to be relevant in the single instances in which they occurred but did not provide evidence for the general safety profile of the medicinal product. No new safety issue on drug interaction, overdose, drug abuse/misuse, pregnancy/lactation, special patient groups or effects of long-term treatment occurred during the period covered by this report.

RMS' comment:

As stated above, the MAH should monitor unlisted interaction cases including colchicine and efalizumab. Based on assessment of pravastatin containing products by the pRMS, the MAH should continue to monitor rhabdomyolysis, cancer, renal failure and respiratory disorders.

Response MAH:

The MAH will closely monitor the undesirable effects and interactions mentioned above.

Clinical expert statement

The MAH states that the product can be safely renewed at the end of a 5-year period for an unlimited period. In their sum, the available case reports did not bring about severe, unexpected reactions, which would point to a new pravastatin-related risk with respect to frequency or nature of unwanted reactions when compared to the unwanted reactions listed in the previous Reference Safety Information.

The possible association of pravastatin (especially long-term therapy) with interstitial lung disease, or nightmares, memory loss and depression in susceptible persons – as reflected in recent scientific publications - has been included as a special warning/precaution into the package leaflet and Summary of Product Characteristics.

The MAH confirms that the authorities have been kept informed of any additional data significant for the assessment of the benefit/risk ratio of the product concerned.

Summary of Product Characteristics, package leaflet and labelling

SPC

The MAH added the sentence “The tablet can be divided into equal halves” to section 3. The RMS agrees with this addition. It has been adequately shown that the tablets can be broken by hand in a reproducible way.

The MAH added the following to section 4.4:

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

The MAH added the following to section 4.8:

Nervous system disorders:

Unknown frequency: nightmares, memory loss, depression

Respiratory, thoracic and mediastinal disorders:

Unknown frequency: Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

RMS' comment:

- 1. Depression should be moved to the SOC Psychiatric disorders. Sexual dysfunction is also part of the PhVWP class labelling for statins and is already listed in the current SPC of pravastatin.*
- 2. Please note that the implementation plan for the class labelling of statins will be discussed during the September 2008 PhVWP. The MAH should submit a new type II variation in case the present SPC proposal does not adequately reflect the PhVWP decision.*
- 3. Pravastatin takes part in the PSUR synchronisation project of the Head of Medicines Agencies. Currently, pravastatin PSURs are being assessed by the p-RMS. As part of the PSUR synchronisation project, a Core Safety Profile (CSP) will be decided on. Once the final p-RMS assessment report has been circulated and the CSP has been agreed, the MAH should compare the agreed CSP with the currently approved SPC(s) and submit variations as required. The variations should be submitted within 60 days of receiving the final p-RMS assessment report and agreed CSP. The final assessment report and agreed CSP can be used as supporting data for these applications.*

Response MAH:

- 1. Depression is moved to the SOC Psychiatric disorders.*
- 2. The MAH has taken notice of the above. The MAH is prepared to submit a new type II variation in case the present SPC proposal does not adequately reflect the upcoming PhVWP decision.*

3. The MAH has taken notice of the above. The MAH is prepared to submit variations as required within 60 days of receiving the final p-RMS assessment report and agreed CSP.

RMS' comment:

The RMS agrees.

Patient Information leaflet

The PIL has already been approved and assessed during a MRP (NL/H/961/01-03/MR). The RMS only requested to add all approved manufacturers for batch release at the end of the PIL. This has been changed by the MAH. The PIL reflects the SPC including all proposed changes as described above.

Readability test of the PIL

The readability test has already been approved and assessed during a MRP (NL/H/961/01-03/MR).

The test was diagnostic. The test consisted of questions which were designed to find out whether the subject was able to locate and understand the question and to act according to the information. Three aspects of readability are distinguished, namely findability, comprehensibility and applicability.

A first test was performed with 10 participants. The second test round was also performed with 10 participants. Both test rounds did not lead to an adaptation of the PIL, although it led to feed-back to further issues but none of them were constituents of failure, according to the MAH. There were sufficient questions (15) about the critical sections of the PIL. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. According to the conclusion of the test, the subjects were able to locate and interpret the requested information correctly. In the test it was easy to determine which results are linked to which conclusions. The conclusions reflect the result. The conclusions are clear, concise and clearly presented.

The user test of the patient information leaflet is of sufficient quality.

Labelling texts

The Labelling text has already been approved and assessed during a MRP (NL/H/961/01-03/MR). Therefore, the RMS does not have any comments with regard to the submitted Labelling texts.

Statement on good manufacturing practice

Manufacturer tablets

The RMS has been assured that acceptable standards of GMP are in place for these product types at all of the sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

Manufacturer active ingredient

Taking into account the review 2001, a new requirement is a GMP declaration that the active ingredient is produced in accordance with the GMP requirements. The qualified person of the manufacturer responsible for batch release, declared that the active ingredient is produced in accordance with the GMP-requirements.

Conclusions, recommendations and commitments

Assessment of the PSUR for pravastatin, period 17 May 2004 to 31 March 2008, dated 13 May 2008, and the Clinical Expert Statement, dated 20 May 2008, led to the following conclusions:

- Submitted data revealed no new safety issues requiring immediate action.
- Renewal was granted by all member states for an indefinite period.

Concerning the PSUR

- Pravastatin takes part in the PSUR synchronisation project of the Head of Medicines Agencies. Currently, pravastatin PSURs are being assessed by the p-RMS. Apart from the MEB's conclusions in this PSUR assessment report, the MAH has committed to act upon the conclusions drawn in the final p-RMS PSUR assessment report.
- The MAH has committed to closely monitor thrombocytopenia, interaction cases including colchicine and efalizumab, cancers, rhabdomyolysis, renal failure, and respiratory disorders.

Concerning the SPC

- The implementation plan for the class labelling of statins will be discussed during the September 2008 PhVWP. The MAH committed to submit a new type II variation in case the present SPC proposal does not adequately reflect the upcoming PhVWP decision.
- Pravastatin takes part in the PSUR synchronisation project of the Head of Medicines Agencies. Currently, pravastatin PSURs are being assessed by the p-RMS. As part of the PSUR synchronisation project, a Core Safety Profile (CSP) will be decided on. Once the final p-RMS assessment report has been circulated and the CSP has been agreed, the MAH committed to compare the agreed CSP with the currently approved SPC(s) and submit variations as required. The variations should be submitted within 60 days of receiving the final p-RMS assessment report and agreed CSP. The final assessment report and agreed CSP can be used as supporting data for these applications.

Other remarks

- In view of the EU worksharing project, the MAH is prepared to adhere to the harmonised birth date and its data lock point. The next PSUR will cover the period 01 April 2008 until the allocated DLP of March 2011 within 60 days from March 2011.

Common Renewal Date

The common renewal date as agreed during the MRP is 9 September 2009. In order to adhere to the EU-Harmonised Birthday Project, the MAH submitted this renewal using the data lock point of 31 March 2008. Therefore, the common renewal date has been advanced to **30 November 2008**.