CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Simvastatine 10 mg, film-coated tablets
Simvastatine 20 mg, film-coated tablets
Simvastatine 40 mg, film-coated tablets
BioOrganics BV, the Netherlands

simvastatin

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/0869/01-03/MR
Registration number in the Netherlands: RVG 33958, 33959, 33960

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Pharmacotherapeutic group:	HMG CoA reductase inhibitors
ATC code:	C10AA01
Route of administration:	oral
Therapeutic indication:	treatment of hypercholesterolaemia or mixed dyslipidaemia, and reduction of cardiovascular mortality and morbidity in risk patients
Prescription status:	prescription only
Date of authorisation in NL:	1 June 2006
Concerned Member States:	Mutual recognition procedure with IT
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 concerned member state has granted a marketing authorisation for Simvastatine 10 mg, film-coated tablets, Simvastatine 20 mg, film-coated tablets and Simvastatine 40 mg, film-coated tablets from BioOrganics BV, the Netherlands. The date of authorisation was on 1 June 2006 in the Netherlands.

The product is indicated for:

- Treatment of 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.

- Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

- Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy.

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

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta hydroxyacid form which has a potent activity in inhibiting HMG CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.
Simvastatin has been shown to reduce both normal and elevated LDL C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL C and reduces plasma TG. As a result of these changes the ratios of total- to HDL C and LDL- to HDL C are reduced.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Zocor 10 mg, 20 mg and 40 mg, film-coated tablets, containing 10, 20 and 40 mg simvastatin, respectively. The innovator product has been registered in the Netherlands by Merck Sharp & Dohme B.V. since 5 December 1988 for the 10, 20 and 40 mg strength (NL License RVG 13193, 13194, 13195), whereas the 80 mg tablet has been registered since 29 June 1999 (NL License RVG 23457). In addition, reference is made to Zocor 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 applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the German reference product Zocor 40 mg tablets by Merck Sharp & Dohme B.V. registered in Germany. 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 simvastatin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white crystalline powder that is freely soluble in alcohol, very soluble in methylene chloride and practically insoluble in water. Simvastatin has seven chiral centres and shows optical rotation. Only one polymorphic form is known, the drug substance is slightly hygroscopic.

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/EMEA 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.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is based on the Ph.Eur. monograph, with additional specifications for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scale batches and 3 blended batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines, demonstrating the stability of the active substance over 36 months. Based on these results, a retest period was granted of 36 months, without specific storage conditions. No photo-instability was observed.

** 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
Simvastatine 10, 20 and 40 mg film-coated tablets contain as active ingredient 10.00, 20.00 and 40.00 mg of simvastatin, respectively. All tablet strengths are white, oblong-shaped, biconvex and scored on one side.

The tablets are supplied in PVC/PE/PVDC/Al blisters and HDPE tablet containers. The blisters are packaged in a cardboard box.

The excipients are
Tablet core - lactose anhydrous, microcrystalline cellulose, pregelatinised maize starch, butylhydroxyanisole, talc (E553b) and magnesium stearate.
Tablet coating - hydroxypropylcellulose, methylhydroxypropylcellulose, titanium dioxide (E171) and talc (E553b).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in a flow chart and narrative in accordance with the relevant European guidelines. The packagings are usual and suitable for the product. The core formulation of the 10, 20 and 40 mg tablets are proportional.

Excipients
The excipients used are common in the manufacture of tablets. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs.

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 production scale batches for each strength in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are based on the monograph for tablets in the Ph.Eur. and include tests for appearance, uniformity of mass (of subdived scored tablets), hardness, disintegration time, water content, dissolution, identification, assay, content uniformity, related substances, antioxidant and microbial contamination. Limits in the specifications 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 for 3 production scale batches for each strength have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product over 48 months have been provided for 6 batches of each strength in accordance with applicable European guidelines. Based on these data, a shelf-life could be granted of 3 years without specific storage conditions.

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

This product is a generic formulation of Zocor, 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 identical products on the market. The approval of this product will not result in an increase in the total quantity of simvastatin 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

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Simvastatine 40 mg is compared with the reference product Zocor 40 mg under fasted conditions. The use of the innovator product as reference products is justified, because of the essentially similar composition of the originator products, and the comparable dissolution profiles.

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

Simvastatin should be taken once daily without reference to food intake. Therefore, 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.

Bioequivalence study
A randomised, open-label, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 48 (4 alternates) healthy volunteers, aged 19-44 years (21 male, 27 female). Each subject received daily a single dose (40 mg) of one of the 2 simvastatin formulations. The tablet was administered with 200 ml water after a 10 h fasting period. For each subject there were 2 dosing periods, separated by a washout period of 10 days. Blood samples were taken predose and at 0.33, 0.67, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hours after administration of the products.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of simvastatin under fasted conditions

Treatment N=46	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	27.9 ± 19.3	35.4 ± 28.6	6.9 ± 5.7	1.0 (0.67-6.0)	10.3 ± 7.5
Reference	28.7 ± 21.0	33.5 ± 26.7	9.2 ± 7.3	1.0 (0.67–4.0)	8.9 ± 10.8
***Ratio (90% CI)**	0.99 (0.87-1.12)	1.06 (0.93-1.22)	0.73 (0.63-0.84)	---	---
CV (%)	36.7	40.6	41.3	---	---

$AUC_{0-\infty}$	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

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of β-hydroxy-simvastatin under fasted conditions

Treatment N=46	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16.5 ± 8.6	19.7 ± 9.0	1.7 ± 1.2	4.0 (2.0-10.0)	9.2 ± 4.9
Reference	15.8 ± 8.5	18.3 ± 9.0	1.7 ± 1.3	4.0 (1.5–12.0)	7.7 ± 4.1
***Ratio (90% CI)**	1.03 (0.95-1.14)	1.07 (0.99-1.16)	1.00 (0.82-1.20)	---	---
CV (%)	22.4	21.5	33.0	---	---

$AUC_{0-\infty}$	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-inf} and C_{max} for β-hydroxy-simvastatin, the main metabolite of simvastatin, are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of β-hydroxy-simvastatin under fasted conditions, it can be concluded that test Simvastatine 40 mg tablet and the German reference Zocor 40 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

For simvastatin, AUC_{0-inf} values were comparable, but C_{max} was 0.75 fold lower after administration of the Simvastatin 40 mg tablet. This was not considered to be clinically relevant. Taking into account that β-hydroxy-simvastatin is the principal molecule responsible for the pharmacologic action, it seems reasonable to conclude that the plasma determinations of β-hydroxy-simvastatin are indicative of clinical efficacy and safety. The difference in C_{max} of simvastatin is not related to the amount of simvastatin which is converted into active metabolites. Therefore, determination of plasma concentrations of simvastatin to correlate to clinical efficacy are of limited value. As expected a large intra-individual variation (CV) was seen.The statistical analysis of the pharmacokinetic data was adequate.

Extrapolation of results
The Simvastatine 10 mg, 20 and 40 mg tablets are dose proportional with each other. The pharmacokinetics of simvastatin is linear in the range of 5 - 120 mg. All doses are manufactured by the same manufacturers and process. The results of the bioequivalence study performed with the 40 mg tablets, therefore apply to the 10 and 20 mg strengths.

The MEB has been assured that the 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
Simvastatin was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of simvastatin 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 applicant 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 Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in line with the harmonised SPC of the Directive 2001/83/EC art. 30 referral for Zocor (CHMP 459/04, version 09/06/04, 28 april 2004) by Merck Sharp & Dohme B.V. and two consecutive type II variations.

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 participants had mostly a mid- or higher education level. The readability test has been acceptably performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Simvastatine 10 mg, Simvastatine 20 mg, and Simvastatine 40 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zocor. Zocor 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. The SPC is consistent with that of the innovator product. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The date of authorisation was on 1 June 2006 in the Netherlands. The concerned member state, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Simvastatine 10 mg, Simvastatine 20 mg and Simvastatine 40 mg tablets with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 12 October 2006.

There was no discussion in the CMD(h). Agreement between the member states was reached during a written procedure.

The PSUR submission cycle is 3 years. The 1st PSUR will cover the period from October 2006 until October 2009.

The date for the first renewal will be 12 October 2011.

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
PL	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
Change in test procedure of the finished product. Other changes to a test procedure, including replacement or addition of a test procedure.	NL/H/869/ 001-003/ IB/001	IB	15-4-2009	14-5-2009	Approval	N
Implementation of change(s) requested by the EMEA/ National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC. Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH	NL/H/869/ 001-003/ IB/002/G	IB/G	17-6-2010	17-7-2010	Approval	Y, Annex I

Annex I – Variation NL/H/869/001-003/IB/002/G

Scope of variation

This was a variation to implement:

- the available paediatric data assessed in the EU Worksharing project of the Co-ordination Group for Mutual Recognition and Decentralised Procedures human (CMD(h))
- the available data assessed by the Pharmacovigilance Working Party (PhVWP) on warnings on adverse events in section 4.4 and 4.8.
- the available data assessed in the EU PSUR-Worksharing project

Many amendments were made to SPC and PIL.
The most important amendments are described below.

Blue = text added
Red = text deleted

SPC

Section 4.2 – Posology and method of administration

The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see sections 4.4 and 5.1).

(…)

Concomitant therapy
Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

In patients taking ciclosporin, danazol, gemfibrozil, or other fibrates (except fenofibrate) ~~or lipid-lowering doses (≥1 g/day) of niacin~~ concomitantly with simvastatin, the dose of simvastatin should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day. In patients taking diltiazem or amlodipine concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day. (see sections 4.4 and 4.5.).

Section 4.4 – Special warnings and precautions before use

Myopathy/Rhabdomyolysis
(…)
In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0 % compared with 0.02 % for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1 %. (See sections 4.8 and 5.1.) ~~, myositis, polymyositis.~~

(…)

Before the treatment
All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

- Elderly (age ~~≥ 70~~ ≥ 65 years)
- Female gender
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

(…)

Whilst on treatment
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
A higher rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy.

(…)

Measures to reduce the risk of myopathy caused by medicinal product interactions (see section 4.5)
(…)
The~~re~~ risk is ~~also a slight~~ increased by concomitant use of ~~in risk when~~ diltiazem or amlodipine ~~is used~~ with simvastatin 80 mg. The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins (see section 4.5.)

(…)

The combined use of simvastatin at doses higher than 40 mg daily with diltiazem or amlodipine should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid modifying doses (□ 1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

(…)

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6 % of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Calcium Channel Blockers

- *Verapamil*
  The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

- *Diltiazem*
  The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

- *Amlodipine*
  Patients on amlodipine treated concomitantly with simvastatin 80 mg have an increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Niacin (nicotinic acid)

Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

~~*Amlodipine*~~

~~In a pharmacokinetic study, concomitant administration with amlodopine resulted in a 1.4 fold increase in the peak concentration (Cmax) and 1.3 increase in the total exposure (area under the concentration –time curve (AUC) of the active metabolites of simvastatin without affecting its cholesterol lowering effect. The clinical relevance of the interaction is unknown.~~

~~*Amiodarone and verapamil*~~

~~The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6 % of patients receiving simvastatin 80 mg and amiodarone.~~

~~An analysis of the available clinical trials showed an approximately 1 % incidence of myopathy in patients receiving simvastatin 40 mg or 80 mg and verapamil. In a pharmacokinetic study, concomitant~~

~~administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.~~

~~*Diltiazem*~~
~~An analysis of the available clinical trials showed a 1 % incidence of myopathy in patients receiving simvastatin 80 mg and diltiazem. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.~~

Section 4.8 – Undesirable effects

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy* (including myositis), rhabdomyolysis with or without acute renal failure, (see section 4.4), myalgia, muscle cramps
*In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0 % vs 0.02 %, respectively).

Section 5.1 – Pharmacodynamic properties

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease
(…)
The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with simvastatin 80 mg versus 20 mg (median follow-up 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; simvastatin 20 mg (n = 1553; 25.7 %) vs. simvastatin 80 mg (n = 1477; 24.5 %); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on simvastatin 80 mg compared with 0.02 % for patients on 20 mg. Approximately half of these myopathy cases occurred during the first year of treatment.

Patient Information Leaflet

Section 2 – Before you take Simvastatin

(…)
Take special care with Simvastatin
Check if one of the warnings listed below applies to you or applied to you in the past. Consult your doctor immediately:
- if you have unexplained muscle pain, muscle tenderness or muscle weakness; you should report this to your doctor immediately, as simvastatin may have a harmful effect on your muscles.
- if you have previously experienced problems with your muscles as a result of the use of statins or fibrates (medicines to reduce fat levels in the blood).
- ~~if you have severe respiratory failure~~
- if you are ~~more than 70~~ 65 years or older.
- if you are female
- if your thyroid does not function well and you are not being treated for it.

- if you or your family members suffer from hereditary muscle disorders.
- if you consume considerable amounts of alcohol.
- if you have an impaired kidney function.
- if you need to have major surgery, your doctor will tell you that treatment with simvastatin must be discontinued temporarily, a few days before major surgery.

(…)

Taking other medicines
(…)
As well as the medicines listed above, tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription. In particular, tell your doctor if you are taking any of the following:

- medicines to prevent blood clots, such as warfarin, phenprocoumon or acenocoumarol (anticoagulants)
- fenofibrate (another medicine for lowering cholesterol)
- niacin (another medicine for lowering cholesterol)
- rifampicin (a medicine used to treat tuberculosis).

Section 3 – How to take Simvastatin
(…)
Combination treatment
(…)
Take a maximum of 40 mg once daily if you have to take simvastatin simultaneously with the following medicines:

- diltiazem (medicine used to treat high blood pressure)
- amlodipine (medicine used to treat high blood pressure and chest pain (angina))