Medicines & Healthcare products Regulatory Agency

Public Assessment Report

Simvastatin 20 and 40 mg granules for oral suspension in sachet

(Simvastatin)

UK Licence No: PL 44710/0025-6

Kinedexe UK Limited

LAY SUMMARY
Simvastatin 20 and 40 mg granules for oral suspension in sachet (simvastatin)

This is a summary of the Public Assessment Report (PAR) for Simvastatin 20 and 40 mg granules for oral suspension in sachet (PL 44710/0025-6). For ease of reading, this medicinal product will be referred to as Simvastatin Oral Suspension in this Lay Summary.

This summary explains how Simvastatin Oral Suspension was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Simvastatin Oral Suspension.

For practical information about using Simvastatin Oral Suspension, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Simvastatin Oral Suspension and what is it used for?

Simvastatin Oral Suspension is a generic medicine. This means that this product is similar to 'reference medicines', already authorised in the UK called ZOCOR® 20mg and 40mg Film-coated Tablets (Merck Sharp & Dohme Ltd; PL 00025/0242-3).

Simvastatin granules for oral suspension is a medicine used to lower levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood and raises level of "good" cholesterol (HDL cholesterol).

How does Simvastatin Oral Suspension work?

Simvastatin oral suspension contains the active substance, simvastatin which belongs to a member of the class of medicines called statins. This medicine works by reducing the amount of cholesterol and fatty substances called triglycerides in the blood. Cholesterol is vital to the normal functioning of the body, but if levels of cholesterol in the bloodstream get too high it can be deposited on the walls of the arteries, where it builds up eventually leading to the blocking of the blood vessel. This medicine lower levels of fat which will reduce the risk of developing heart disease.

How is Simvastatin Oral Suspension used?

Simvastatin oral suspension is taken orally. This medicine can be taken with or without food in the evening.

The granules should be mixed in half a glass of water (approximately 125ml) and should be taken immediately after mixing. If some granules remain in the glass, add sufficient amount of water stir it and drink it completely in order to get the complete dose.

The patient should stay on a cholesterol-lowering diet while taking Simvastatin granules for oral suspension.

The recommended dose is 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg by mouth once a day.
Simvastatin granules for oral suspension should only be used by patients who are prescribed a 20 mg or 40 mg dose of simvastatin, respectively.

The usual starting dose in adults is 10 mg, 20 mg or in some cases, 40 mg a day. A doctor may adjust the dose after at least 4 weeks to a maximum of 80 mg a day.

Patients must not take more than 80 mg a day.

A doctor may prescribe lower doses, particularly if patients are taking certain medicinal products or have certain kidney conditions.

The 80 mg dose is only recommended for adult patients with very high cholesterol levels and at high risk of heart disease problems who have not reached their cholesterol goal on lower doses.

For children (10-17 years old), the recommended usual starting dose is 10 mg a day in the evening. The maximum recommended dose is 40 mg a day. It is to be noted that Simvastatin granules for oral suspension are recommended for doses of 20 mg or more.

If a doctor has prescribed Simvastatin for oral suspension along with another medicine for lowering cholesterol containing any bile acid sequestrant, patients should take Simvastatin for oral suspension at least 2 hours before or 4 hours after taking the bile acid sequestrant.

Simvastatin Oral Suspension can only be obtained with a prescription from a doctor.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

How has Simvastatin Oral Suspension been studied?
Because Simvastatin Oral Suspension is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, ZOCOR® 20 mg and 40 mg Film-coated Tablets (Merck Sharp & Dohme Ltd). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Simvastatin Oral Suspension?
Because Simvastatin Oral Suspension is a generic medicine, and is bioequivalent to the reference medicine, ZOCOR® 20 mg and 40 mg Film-coated Tablets (Merck Sharp & Dohme Ltd), its benefits and risks are taken as being the same as the reference medicines.

Why is Simvastatin Oral Suspension approved?
It was concluded that, in accordance with EU requirements, Simvastatin Oral Suspension has been shown to have comparable quality and to be bioequivalent to ZOCOR® 20 mg and 40 mg Film-coated Tablets (Merck Sharp & Dohme Ltd). Therefore, the view was that, as for ZOCOR® 20 mg and 40 mg Film-coated Tablets (Merck Sharp & Dohme Ltd), the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Simvastatin Oral Suspension?
A risk management plan has been developed to ensure that Simvastatin Oral Suspension is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the PIL for Simvastatin Oral Suspension, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Simvastatin Oral Suspension
A Marketing Authorisation for Simvastatin Oral Suspension was granted on 13 September 2018.

The full PAR for Simvastatin Oral Suspension follows this summary.

This summary was last updated in November 2018.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Kinedexe UK Limited Marketing Authorisations for the medicinal products Simvastatin 20 and 40 mg granules for oral suspension in sachet (PL 44710/0025-6) on 13 September 2018.

These products are 'prescription only medicines' (legal status "POM"), used for the following indications:

Hypercholesterolaemia

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

Cardiovascular prevention

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

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to ZOCOR® 20mg and 40mg Film-coated Tablets, which were granted Marketing Authorisations to Merck Sharp & Dohme Ltd (PL 00025/0242-3) on 28 April 1989.

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.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

One bioequivalence study (conducted under fasting conditions) was submitted to support these applications. The bioequivalence study is stated to have been conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of the originator products that have been in clinical use for over 10 years.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with these applications, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Simvastatin 20 and 40 mg granules for oral suspension in sachet outweigh the risks and Marketing Authorisations were granted.

II Quality Aspects

II.1 Introduction

The finished product is formulated as granules for oral suspension in sachet. Each sachet contains 20 mg or 40 mg of simvastatin, as active ingredient. The excipients present are lactose monohydrate, butyl hydroxyanisole (E320), citric acid monohydrate, Di-sodium phosphate anhydrous, sodium lauryl sulphate, sucrose, acesulfame potassium, strawberry flavour (which also contains flavouring substances, natural flavouring substances, flavouring preparations, maltodextrin, arabic gum (E414), triethyl citrate (E1505), propylene glycol (E1520), ascorbic acid (E300), butylated hydroxyanisole (E320) and benzyl alcohol (E1519)).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of strawberry flavour which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in aluminium foil laminated sachet. Each carton contains 28 sachets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN: Simvastatin

Chemical Name:

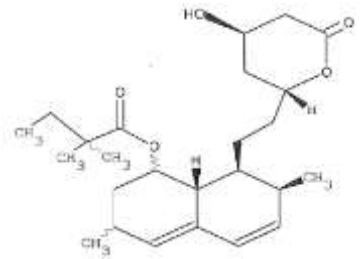
(1S,3R,7S,8S,8aR)-8-[2-[2R,4R)-4-Hydroxy-6-oxo-tetrahydro-2H-pyran-2 yl]ethyl]-3,7 dimethyl-1 ,2,3, 7 ,8,8a-hexahydronaphthalen-1-yl 2,2 dimethylbutanoate.

Butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a,hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6 oxo-2H pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-(1α,3α,7β,8β(2S*,4S*),8aβ))

2,2-Dimethylbutyric acid,8-ester with (4R,6R)-6-2-[(1 S,2S,6R,8S,8αR)-1 ,2,6, 7,8,8ahexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

[IS-[1α,3α,7β,8β(2S* ,4S*),8aβ]]-2,-2-Dimethylbutanoic acid l ,2,3,7 ,8,8a-Hexahydro-3,7 dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester. Synvinolin; Velastatin

Structure:



Molecular formula: $C_{25}H_{38}O_5$

Molecular weight: 418.6 g/mol

Appearance: A white to off-white powder.

Solubility: Simvastatin is practically insoluble in water, freely soluble in chloroform, methanol and alcohol, sparingly soluble in propylene glycol and very slightly soluble in hexane.

Simvastatin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, simvastatin, are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious oral suspension in a sachet containing 20 mg or 40 mg of simvastatin, that is a generic version of the reference products ZOCOR® 20mg and 40mg Film-coated Tablets (Merck Sharp & Dohme Ltd; PL 00025/0242-3).

Comparative *in vitro* dissolution profiles have been provided between the test and reference products.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. A validation report for commercial scale batches has been provided. The process validation data provided are satisfactory.

Finished Product Specification

The proposed finished product specifications are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years with no special storage conditions is set.

Suitable post approval stability commitments have been provided that stability testing will be continued on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III Non-Clinical Aspects

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of simvastatin are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The Applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for these product types. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for these product types. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for these product types. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since these products are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV Clinical Aspects
IV.1 Introduction
The clinical pharmacology of simvastatin is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of simvastatin.

Based on the data provided, Simvastatin 20 mg and 40 mg Granules for Oral Suspension can be considered bioequivalent to ZOCOR® 20 mg and 40mg Film-coated Tablets (Merck Sharp & Dohme Limited).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence study:

An open-label, balanced, randomised, two-treatment, four-period, two-sequence, full replicate, single dose, crossover, oral bioequivalence study of Simvastatin 40 mg Granules for Oral Suspension and ZOCOR® 40mg Film-coated Tablets (Merck Sharp & Dohme Limited) in healthy, adult, human subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a dose 40mg of the test suspension or one tablet (40 mg) of the reference product with 240 mL of water.

The subjects received standard meals at about 10.50 hours pre-dose and at 04.00, 08.00, 12.00, 24.00 hours after dosing in each period. There was a washing period of 7 days between the different phases of the study.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days.

The bioequivalence study had a replicate design and for simvastatin the within-subject variability for C_{max} of the reference compound in the study was found to be >30%. Hence, the acceptance criteria for C_{max} were widened to 70.34% - 142.16% based on the observed within-subject variability.

The pharmacokinetic results are presented below:

Parameter		C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)
N		36	36	36
Geometric LSM	T	17.6085	73.1594	76.7201
	R	20.4457	80.6866	86.9559
T/R Ratio (%):		86.12%	90.67%	88.23%
90% Confidence Interval:		77.00% -96.32%	83.24%-98.76%	80.83%-96.31%
BE acceptance criteria		70.34% - 142.16%	80.00%-125.00%	80.00%-125.00%
p-values (ANOVA):				
Sequence		0.0017	0.1600	0.3231
Subject (sequence)		<.0001	<.0001	<.0001
Period		0.6714	0.4271	0.4002
Treatment		0.0290	0.0600	0.0196
Intra-subject Variability:		41.4	31.1	31.9
Power (%)		94.9%	99.6%	99.4%

Furthermore, the beta-hydroxyacid metabolite was also measured and the results were consistent with the findings for simvastatin.

Study conclusion
The 90% confidence intervals of the test/reference ratio for AUC_{0-t} and C_{max} values for simvastatin lie within the acceptable limits, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product Simvastatin 40 mg Granules for Oral Suspension is bioequivalent to the reference product and ZOCOR® 40mg Film-coated Tablets (Merck Sharp & Dohme Limited).

As the 20 mg and 40 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 40 mg granules for oral suspension can be extrapolated to the 20 mg strength oral suspension.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety
No new data on clinical safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system
The Marketing Authorisation Holder (MAH) has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and

interventions designed to identify, characterise, prevent or minimise risks relating to Simvastatin 20 and 40 mg granules for oral suspension in sachet.

A summary of safety concerns as approved in the RMP, is listed below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to the active substance or to any of the excipients • Hepatotoxicity and hepatic failure • Myopathy/rhabodomyolysis • Increased toxicity and myositis/rhabdomyolysis due to drug interactions with potent inhibitors of CYP3A4 • Increased toxicity and myositis/rhabdomyolysis due to drug interactions with calcium channel blockers and fibrates (except fenofibrates) • Increased toxicity and myositis/rhabdomyolysis due to interaction with grapefruit juice • Diabetes mellitus • Interstitial lung disease • Gastrointestinal malabsorption and discomfort in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose galactose malabsorption • Effects on the baby with exposure during pregnancy
Important potential risks	• None
Missing information	• None

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended for these applications, from a clinical point of view.

V User consultation

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, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant's products and the reference products. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Simvastatin 20 and 40 mg granules for oral suspension in sachet is presented below:


28 Sachets
40 mg
Simvastatin
40mg granules
for oral suspension in sachet
Simvastatin
40mg granules
for oral suspension
in sachet
28 Sachets
40 mg
Each sachet contains 40mg of simvastatin.
Also contains lactose, sucrose and benzyl alcohol E1519.
28 Sachets, granules for oral suspension in sachet
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Use as directed by your physician.
The granules should be mixed in half a glass of water (approx. 125ml) and should be taken immediately after mixing. If some granules remains in the glass add sufficient amount of water stir it and drink it completely in order to get the complete dose.
Simvastatin
40mg granules
for oral suspension
in sachet
28 Sachets
KinedexE
POM
87 mm


Read the package leaflet before use.
The granules should be mixed in half a glass of water (approx. 125ml) and should be taken immediately after mixing. If some granules remains in the glass add sufficient amount of water stir it and drink it completely in order to get the complete dose.
Simvastatin
40mg granules
for oral suspension
in sachet
For oral administration
40 mg

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome