SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Simva-Denk 20
Simva-Denk 40

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: simvastatin

Simva-Denk 20
Each film-coated tablet contains 20 mg simvastatin.
Excipients with known effect: Each film-coated tablet contains 144.42 mg of lactose monohydrate and less than 1 mmol sodium (23 mg).

Simva-Denk 40
Each film-coated tablet contains 40 mg simvastatin.
Excipients with known effect: Each film-coated tablet contains 288.84 mg of lactose monohydrate and less than 1 mmol sodium (23 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Simva-Denk 20
Yellow-brown, oblong film-coated tablet with a one-sided break-line, lateral notches and with intact coating.

Simva-Denk 40
Light pink, oval-shaped film-coated tablet with one-sided break-line, lateral notches and with intact coating.

The film-coated tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
For treatment of primary or mixed hyperlipidaemia as an adjunct to diet when diet and other non-pharmacological measures alone (e.g. physical exercise and weight reduction) are inadequate.

For treatment of homozygous familial hypercholesterolaemia (HoFH). Simvastatin is used as an adjunct to diet and other lipid-lowering measures (e.g. LDL [low density lipoprotein] apheresis) or if such measures are not appropriate.

Cardiovascular prevention
For 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 cardioprotective therapy (see section 5.1).

4.2 Posology and method of administration

Posology
The dosage range is 5 mg - 80 mg simvastatin per day, given orally as a single dose in the evening. Dose adjustments, if required, should be implemented at intervals of no less than 4 weeks, up to a maximum of 80 mg simvastatin once daily given as a single dose in the evening. The 80 mg dose is recommended only in patients with severe hypercholesterolaemia at high risk of cardiovascular complications who have not achieved their treatment objective on a lower dose and when the benefit of treatment is expected to outweigh the potential risks (see sections 4.4 and 5.1).

Hypercholesterolaemia
The patient should be following a suitable lipid-lowering diet and continue it during treatment with simvastatin. The usual starting dose is 10 mg to 20 mg simvastatin once daily as a single dose in the evening. Patients who require a large reduction in LDL cholesterol (more than 45%) may be started at a dose of 20 mg to 40 mg simvastatin once daily as a single dose in the evening. Dose adjustments, if required, should be implemented as described above.

Homozygous familial hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended starting dose is 40 mg simvastatin once daily taken in the evening. Simvastatin should be used as an adjunct to other lipid-lowering measures (e.g. LDL apheresis) in these patients or without such measures if they are unavailable.

In patients taking lomitapide concomitantly with simvastatin, a dose of 40 mg simvastatin per day must not be exceeded (see sections 4.3, 4.4 and 4.5).

Cardiovascular prevention
In patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia), the usual dose is 20 mg to 40 mg simvastatin per day as a single dose in the evening. Drug therapy can be initiated simultaneously with diet and physical exercise. Dose adjustments, if required, should be implemented as described above.

Concomitant administration with other medicinal products
Simvastatin is effective alone or in combination with anion exchangers. Simvastatin should be taken either at least 2 hours before or at least 4 hours after administration of an anion exchanger.

In patients taking simvastatin concomitantly with fibrates other than gemfibrozil (see section 4.3) or fenofibrate, a dose of 10 mg simvastatin per day should not be exceeded. In patients taking amiodarone, amlodipine, verapamil, diltiazem or medicinal products containing elbasvir or grazoprevir concomitantly with simvastatin, a dose of 20 mg simvastatin per day should not be exceeded (see sections 4.4 and 4.5).

Renal impairment
Usually, no dose adjustments are necessary in patients with moderately impaired renal function. In patients with severely impaired renal function (creatinine clearance under 30 ml/min), doses over 10 mg per day should be carefully considered and, if deemed necessary, prescribed cautiously.

Elderly patients
No dose adjustment is required for elderly patients.

Paediatric population
For children and adolescents (boys: Tanner stage II and above; girls: at least 1 year post-menarche, 10-17 years of age) with heterozygous familial hypercholesterolaemia, the usual recommended dose is 10 mg per day as a single dose in the evening at the beginning of treatment. Children and adolescents should follow a cholesterol-lowering diet before initiation of treatment with simvastatin; this diet should be continued

during treatment with simvastatin.

The recommended dosage range is 10 mg - 40 mg simvastatin per day; the maximum recommended dose is 40 mg per day. Doses should be individualised according to the recommended goal of therapy as per the paediatric treatment recommendations (see sections 4.4 and 5.1). Dosage adjustments should be implemented at intervals of no less than 4 weeks.
Experience with simvastatin in prepubertal children is limited.

Method of administration
Simvastatin is taken orally. Simvastatin can be taken as a single dose in the evening.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active liver disease or unexplained persistent elevation of serum transaminases.
- Pregnancy and lactation (see section 4.6).
- Concomitant use of potent CYP3A4 inhibitors (substances increasing the AUC by at least approximately 5-fold) (e.g. itraconazole, ketoconazole, posaconazole voriconazole, HIV protease inhibitors [e.g. nelfinavir], boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat) (see sections 4.4 and 4.5).
- Concomitant use of gemfibrozil, ciclosporin or danazol (see sections 4.4 and 4.5).
- Concomitant use of lomitapide and simvastatin in doses higher than 40 mg in patients with homozygous familial hypercholesterolaemia (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

Myopathy/rhabdomyolysis
Simvastatin, like other HMG-CoA reductase inhibitors, occasionally causes myopathy manifesting as muscle pain, sensitivity or weakness in association with creatine kinase (CK) elevations (> ten times the upper limit of normal). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, very rarely with a fatal outcome. The risk of myopathy is increased in patients with high levels of HMG-CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see section 4.5).

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose-dependent. In a clinical trial database, 41,413 patients treated with simvastatin were documented, 24,747 (approximately 60%) of them in studies with a median follow-up duration of at least 4 years.
The incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20 mg, 40 mg and 80 mg simvastatin per day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In one clinical trial, patients with a history of myocardial infarction were treated with 80 mg simvastatin per day (mean follow-up duration 6.7 years). The incidence of myopathy was approximately 1.0%, as compared to 0.02% in 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 was approximately 0.1% (see sections 4.8 and 5.1).

Compared to other statin-based therapies with similar LDL-lowering efficacy, the risk of myopathy is greater in patients on a daily dose of 80 mg simvastatin. Therefore, a daily dose of 80 mg simvastatin should be used only in patients with severe hypercholesterolemia and at high risk of cardiovascular complications who have not achieved their treatment objective on lower doses and when the benefit is expected to outweigh the potential risks. In patients taking a daily dose of 80 mg simvastatin who require an interacting medicinal product in addition, a lower dose of simvastatin or an alternative statin-based therapy with less potential for

drug interactions should be used (see below *Measures to reduce the risk of myopathy caused by drug interactions* and sections 4.2, 4.3, and 4.5).

In a clinical trial in which patients at high cardiovascular risk were treated with 40 mg simvastatin per day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n = 7,367), as compared to 0.24% for Chinese patients (n = 5,468). Although the only Asian population investigated and analysed in this clinical trial was Chinese, simvastatin should in general only be prescribed with caution and at the lowest dose necessary in Asian patients.

Reduced function of transport proteins
Reduced function of the hepatic OATP transport protein can increase the systemic exposure to simvastatin acid and the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicinal products (e.g. ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele c.521T>C coding for a less active OATP1B1 protein have an increased systemic exposure to simvastatin acid and increased risk of myopathy. The risk of myopathy caused by a high dose (80 mg) of simvastatin is about 1% in general, without genetic testing. Based on the results of the SEARCH trial, homozygous C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygous C allele carriers (CT) is 1.5%. The risk in patients with the most common genotype (TT) is 0.3% (see section 5.2). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses should be avoided in identified carriers of the CC genotype. However, an absence of this gene upon genotyping does not rule out the possibility of myopathy occurring.

Creatine kinase (CK) measurements
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> five-fold the upper limit of normal), a repeat measurement should take place after 5-7 days to confirm the results.

Before the start of treatment
All patients who are starting therapy with simvastatin or whose dose of simvastatin is increased, should be informed about the risk of myopathy and requested to report promptly any unexplained muscle pain, sensitivity or weakness.

Caution should be exercised in patients with risk factors for rhabdomyolysis. In order to establish a reference baseline value, CK levels should be measured before the start of treatment in the following situations:

- Elderly patients (≥ 65 years old)
- Female patients
- Renal impairment
- Untreated hypothyroidism
- Personal or family history of hereditary muscular disorders
- History of muscle symptoms during treatment with statins or fibrates
- Alcohol abuse.

In such cases, a careful benefit/risk appraisal regarding the treatment is recommended. The patients concerned should be closely monitored. In patients who have previously experienced myopathy during treatment with fibrates or statins, treatment with a different substance in this class should be initiated with caution. If CK levels are significantly higher than baseline (> five-fold the upper limit of normal), treatment should not be started.

During the course of treatment
If muscle pain, weakness or cramps occur during treatment with a statin, CK levels should be measured. If CK levels are significantly elevated (> five-fold the upper limit of normal) in the absence of strenuous exercise, treatment should be discontinued. If muscular symptoms are serious and debilitating, treatment discontinuation should be considered even if CK levels are elevated to less than five times the upper limit of normal. If myopathy is suspected for any other reason, treatment should be discontinued.

There have been very rare reports of immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase levels that persist despite discontinuation of statin treatment (see section 4.8).

If symptoms resolve and CK levels return to baseline, re-initiation of treatment with the same statin or an alternative statin may be considered at the lowest dose and with close monitoring.

An increased rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). It is recommended that CK levels be monitored periodically; this might be useful to identify cases of myopathy without any clinical symptoms. However, such monitoring is not guaranteed to prevent myopathy.

Therapy with simvastatin should be temporarily stopped a few days prior to planned surgery or when major acute symptoms develop or when surgical procedures become necessary.

Measures to reduce the risk of myopathy caused by drug interactions (see also section 4.5)
The risk of myopathy and rhabdomyolysis is significantly increased in cases of concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors [e.g. nelfinavir], boceprevir, telaprevir, nefazodone and medicinal products containing cobicistat), as well as gemfibrozil, ciclosporin and danazol. Concomitant use of simvastatin and medicinal products containing these active substances is contraindicated (see section 4.3).

The risk of myopathy and rhabdomyolysis is also increased in cases of concomitant use of amiodarone, amlodipine, verapamil or diltiazem with certain doses of simvastatin (see sections 4.2 and 4.5). The risk of myopathy including rhabdomyolysis may be increased by concomitant use of fusidic acid and statins. In patients with homozygous familial hypercholesterolaemia (HoFH), this risk may be increased by concomitant use of simvastatin and lomitapide (see section 4.5).

Consequently, regarding CYP3A4 inhibitors, concomitant use of simvastatin and itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat is contraindicated (see sections 4.3 and 4.5). If treatment with potent CYP3A4 inhibitors (substances that increase AUC by approximately the 5-fold or greater) is unavoidable, therapy with simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil and diltiazem (see sections 4.2 and 4.5).
Concomitant intake of grapefruit juice should be avoided during treatment with simvastatin.

Concomitant use of simvastatin and gemfibrozil is contraindicated (see section 4.3). Due to the increased risk of myopathy and rhabdomyolysis, a dose of 10 mg simvastatin per day should not be exceeded in patients concomitantly treated with other fibrates except for fenofibrate (see sections 4.2 and 4.5).
Caution should be exercised when prescribing fenofibrate with simvastatin, as either of these medicinal products can cause myopathy in monotherapy.

Simvastatin must not be co-administered with systemic pharmaceutical forms of fusidic acid, including within 7 days of discontinuing treatment with fusidic acid. In patients in whom the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of treatment with fusidic acid. There have been reports of rhabdomyolysis (including some cases with a fatal outcome) in

patients receiving fusidic acid and statins in combination (see section 4.5). The patients should be advised to seek medical advice immediately if they experience any signs of muscle weakness, pain or sensitivity. Statin therapy may be re-initiated 7 days after the last dose of fusidic acid. In exceptional circumstances in which prolonged systemic administration of fusidic acid is needed, e.g. for the treatment of severe infections, co-administration of simvastatin and fusidic acid should be considered only on a case-by-case basis and under close medical supervision.

The combination of simvastatin at doses higher than 20 mg per day with amiodarone, amlodipine, verapamil or diltiazem should be avoided. Concomitant use of simvastatin in doses higher than 40 mg and lomitapide must be avoided in patients with homozygous familial hypercholesterolaemia (HoFH) (see sections 4.2, 4.3 and 4.5).

Patients taking simvastatin concomitantly with other medicinal products that are moderate CYP3A4 inhibitors in therapeutic doses may have an increased risk of myopathy, particularly at higher simvastatin doses. When co-administering simvastatin with a moderate CYP3A4 inhibitor (substances that increase AUC by approximately two- to five-fold), a dose adjustment may be necessary. For certain moderate CYP3A4 inhibitors, e.g. diltiazem, it is recommended not to exceed a maximum daily dose of 20 mg simvastatin (see section 4.2).

Simvastatin is a substrate of the BCRP (breast cancer resistant protein) efflux transporter. Concomitant use with medicinal products from the BCRP inhibitors class (e.g. elbasvir and grazoprevir) may result in increased plasma concentrations of simvastatin and thus an increased risk of myopathy. Consequently, an adjustment of the simvastatin dose should be considered, depending on the prescribed dose. Concomitant use of elbasvir and grazoprevir with simvastatin has not been investigated. **However, a maximum daily dose of 20 mg simvastatin should not be exceeded in patients who concomitantly receive medicinal products containing the active substances elbasvir or grazoprevir** (see section 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with the combination of HMG-CoA reductase inhibitors and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid); either of these substances can cause myopathy when given alone.

In a clinical trial (median follow-up 3.9 years) in patients with a high cardiovascular risk and well-controlled LDL cholesterol levels receiving simvastatin 40 mg/day with or without ezetimibe 10 mg, no additional benefit regarding cardiovascular outcome was observed after the addition of niacin (nicotinic acid) in lipid-lowering doses (≥ 1 g/day). Physicians contemplating combined therapy with simvastatin and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid) should therefore conduct a careful benefit-risk analysis and should closely monitor patients for any signs and symptoms of muscle pain, sensitivity, or weakness, particularly during the initial months of therapy and when the dose of one substance or both is increased.

Furthermore, in this trial, the incidence of myopathy in Chinese patients receiving simvastatin 40 mg or ezetimibe/simvastatin 10 mg/40 mg was approximately 0.24%, as compared to 1.24% in Chinese patients receiving simvastatin 40 mg or ezetimibe/simvastatin 10 mg/40 mg additionally treated with modified-release nicotinic acid/laropiprant 2,000 mg/40 mg. Although the only Asian population investigated and analysed in this clinical trial was Chinese, and the incidence of myopathy is higher in Chinese patients as compared to non-Chinese patients, concomitant use of simvastatin with lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid) is generally not recommended in Asian patients.

The active substance acipimox is structurally related to niacin. Although acipimox has not been investigated, the risks of myotoxic effects could be similar to those with niacin.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend simvastatin in patients taking daptomycin

unless the benefits of concomitant administration outweigh the risk. Consult the prescribing information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin) and for further guidance related to monitoring (see section 4.5.).

Hepatic effects
In clinical trials, persistent increases (to more than three times the upper limit of normal) in serum transaminases have been observed in some adult patients receiving simvastatin. When simvastatin was interrupted or discontinued, transaminase levels usually slowly returned to baseline levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. In patients titrated to the 80 mg dose, an additional measurement should be performed prior to increasing dose, three months after the increase to the 80 mg dose, and periodically thereafter (e.g. semi-annually) during the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels; in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels continue to rise, particularly if they rise to three times the upper limit of normal and are persistent, simvastatin should be discontinued. It should be noted that ALT may be released from muscle tissue. Therefore, ALT rising with CK may indicate myopathy (see above *Myopathy/rhabdomyolysis*).

There have been rare post-marketing reports of sometimes fatal hepatic failure in patients taking statins, including simvastatin. If serious liver impairment with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with simvastatin, treatment must be promptly discontinued.
If no other cause is found, treatment with simvastatin must not be continued.

The medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate elevations (to less than three times the upper limit of normal) of serum transaminases have been reported during therapy with simvastatin. These changes occurred soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and discontinuation of treatment was not required.

Diabetes mellitus
Some evidence suggests that statins as a substance class raise blood glucose levels and in some patients at high risk of future diabetes mellitus may produce hyperglycaemia requiring adequate diabetes treatment. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for discontinuing statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI > 30 kg/m^2, elevated triglycerides, hypertension) should be monitored both clinically and with respect to the relevant laboratory levels in accordance with national guidelines.

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

Paediatric population
The safety and efficacy of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys at Tanner stage II and above and in girls who were at least 1 year post-menarche. The undesirable effect profile in patients treated with simvastatin was generally consistent with that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there were no signs of effects on growth or sexual development in adolescent boys or girls or any changes regarding menstrual cycle length in girls (see sections 4.2, 4.8, and 5.1). Adolescent girls should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6). In patients aged under

18 years, efficacy and safety have not been studied for treatment periods greater than 48 weeks. Long-term effects on physical, intellectual, and sexual development are currently unknown. Simvastatin has not been studied in patients younger than 10 years of age, or in prepubertal children and premenarchal girls.

This medicine contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Simva-Denk contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Interaction studies have been performed only in adults.

Pharmacodynamic interactions
Interactions with lipid-lowering medicinal products that can cause myopathy in monotherapy
The risk of myopathy including rhabdomyolysis is increased during concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased plasma levels of simvastatin (see below *Pharmacokinetic interactions* and sections 4.3 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each substance alone. Adequate pharmacovigilance and pharmacokinetic data for other fibrates are not available.
Rare cases of myopathy/rhabdomyolysis have been associated with the combination of simvastatin and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid) (see section 4.4).

Pharmacokinetic interactions
Prescribing recommendations for interacting medicinal products are summarised in the table below (see Table 1; further details are explained in the text; see also sections 4.2, 4.3 and 4.4).

Table 1:
Drug interactions associated with increased risk of myopathy/rhabdomyolysis

Interacting substances	**Prescribing recommendations**
Potent CYP3A4 inhibitors, such as Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone	**Concomitant use with simvastatin is contraindicated**

Cobicistat Ciclosporin Danazol Gemfibrozil	
Other fibrates (except fenofibrate)	Do not exceed a dose of 10 mg simvastatin daily
Fusidic acid	Use not recommended with simvastatin
Niacin (nicotinic acid) (≥ 1 g/day)	Use with simvastatin not recommended in Asian patients
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed a dose of 20 mg simvastatin daily
Lomitapide	In patients with homozygous familial hypercholesterolaemia (HoFH), a dose of 40 mg simvastatin per day must not be exceeded.
Daptomycin	It should be considered to temporarily suspend simvastatin in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Grapefruit juice	Avoid grapefruit juice during treatment with simvastatin

Effects of other medicinal products on simvastatin

Interactions with CYP3A4 inhibitors

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy.

Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, and medicinal products containing cobicistat. Concomitant use of itraconazole resulted in a more than ten-fold increase in exposure to simvastatin (active beta hydroxy acid metabolite). Telithromycin caused an eleven-fold increase in exposure to simvastatin acid.

Concomitant use of simvastatin with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat as well as gemfibrozil, ciclosporin and danazol is therefore contraindicated (see section 4.3). If treatment with potent CYP3A4 inhibitors (substances that increase AUC by approximately the 5-fold or greater) is unavoidable, therapy with simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil or diltiazem (see sections 4.2 and 4.4).

Fluconazole

Rare cases of rhabdomyolysis have been reported for concomitant administration of simvastatin and fluconazole (see section 4.4.).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant use of ciclosporin with simvastatin. Concomitant use of ciclosporin is therefore contraindicated (see sections 4.3 and 4.4). Although the mechanism is not fully understood yet, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably in part due to inhibition of CYP3A4 and/or OATP1B1.

Danazol
The risk for myopathy/rhabdomyolysis is increased by concomitant use of danazol with simvastatin. Concomitant use of danazol is therefore contraindicated (see sections 4.3 and 4.4).

Gemfibrozil
Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or of OATP1B1 (see sections 4.3 and 4.4). Concomitant administration of gemfibrozil is contraindicated.

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased in the case of concomitant systemic administration of fusidic acid and statins. The underlying mechanism of this interaction (be it pharmacodynamic or pharmacokinetic or both) is yet unknown. There have been reports of rhabdomyolysis (including some with a fatal outcome) in patients receiving this combination. Concomitant administration of this combination may result in increased plasma levels of both substances. If systemic treatment with fusidic acid is required, treatment with simvastatin must be discontinued throughout the duration of treatment with fusidic acid. **See also section 4.4.**

Amiodarone
The risk of myopathy and rhabdomyolysis is increased in the case of concomitant use of amiodarone and simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients taking 80 mg simvastatin and amiodarone. Therefore, the dose of simvastatin should not exceed 20 mg per day in combination with amiodarone.

Calcium channel blockers

- *Verapamil*
  The risk of myopathy and rhabdomyolysis is increased in cases of concomitant use of verapamil and 40 mg or 80 mg simvastatin (see section 4.4).
  In a pharmacokinetic study, concomitant use with verapamil resulted in a 2.3-fold increase in exposure to simvastatin acid, presumably in part due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg per day in combination with verapamil.

- *Diltiazem*
  The risk of myopathy and rhabdomyolysis is increased in cases of concomitant use of diltiazem and 80 mg simvastatin (see section 4.4). In a pharmacokinetic study, concomitant use with diltiazem resulted in a 2.7-fold increase in exposure to simvastatin acid, presumably in part due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg per day in combination with diltiazem.

- *Amlodipine*
  Patients on amlodipine concomitantly receiving simvastatin have an increased risk of myopathy. In a pharmacokinetic study, concomitant use with amlodipine caused an approximately 1.6-fold increase in exposure to simvastatin acid. Therefore, the dose of simvastatin should not exceed 20 mg per day in combination with amlodipine.

Lomitapide
The risk of myopathy and rhabdomyolysis may be increased by concomitant use of lomitapide and simvastatin (see sections 4.3 and 4.4). Therefore, a dose of 40 mg simvastatin must not be exceeded in patients with homozygous familial hypercholesterolaemia (HoFH) receiving lomitapide.

Moderate CYP3A4 inhibitors
Patients taking simvastatin concomitantly with other medicinal products that are moderate CYP3A4 inhibitors in therapeutic doses may have an increased risk for myopathy, particularly at higher simvastatin doses (see section 4.4).

Inhibitors of the transport protein OATP1B1
Simvastatin acid is a substrate for the transport protein OATP1B1. Concomitant use of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and thus an increased risk of myopathy (see sections 4.3 and 4.4).

BCRP (breast cancer resistant protein) inhibitors
Concomitant use with medicinal products from the BCRP inhibitors class including medicinal products containing elbasvir or grazoprevir may result in increased plasma concentrations of simvastatin and thus an increased risk of myopathy (see sections 4.2 and 4.4).

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

Grapefruit juice
Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Colchicine
There have been reports of myopathy and rhabdomyolysis in patients with impaired renal function concomitantly receiving colchicine and simvastatin. Close clinical monitoring of such patients taking this combination is advised.

Daptomycin
The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g. simvastatin) and daptomycin (see section 4.4).

Rifampicin
Since rifampicin is a potent CYP3A4 inducer, patients receiving long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience decreased efficacy of simvastatin. In a pharmacokinetic study in healthy volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93% in the case of concomitant use of rifampicin.

Effects of simvastatin on the pharmacokinetics of other medicinal products
Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is also not expected to affect plasma concentrations of substances metabolised via CYP3A4.

Oral anticoagulants
In two clinical trials, one performed in healthy volunteers and the other in patients with hypercholesterolaemia, simvastatin 20-40 mg/day moderately enhanced the effect of coumarin-derivative anticoagulants. The prothrombin time, expressed as International Normalised Ratio (INR), increased from 1.7 to 1.8 in volunteers and from 2.6 to 3.4 in patients. Very rare cases of elevated INR have been reported. In patients taking coumarin derivatives, prothrombin time should therefore be determined at the beginning of therapy with simvastatin and subsequently at frequent intervals to ensure that no significant alteration of prothrombin time occurs. Once levels have stabilised, it is recommended to subsequently determine prothrombin time at intervals in line with common practice for patients treated with coumarin derivatives. If the dose of simvastatin is modified or simvastatin is discontinued, the same procedure should be followed. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

4.6 Fertility, pregnancy and lactation

Pregnancy
Simvastatin is contraindicated during pregnancy (see section 4.3).

The safety of simvastatin in pregnant women has not been investigated. No controlled clinical studies with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors are available. In an analysis of experience to date in approximately 200 women who had mistakenly taken simvastatin or a structurally related HMG-CoA reductase inhibitor during the first trimester of pregnancy, the risk of congenital anomalies was not increased as compared to that of the general population. This sample size was statistically sufficient to exclude a 2.5-fold or greater increase in risk as compared to the incidence to be expected for the general population.

Although there is no evidence that the incidence of congenital anomalies in children of mothers taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonic acid, which plays a role as a cholesterol synthesis precursor. As atherosclerosis is a chronic disease, discontinuation of lipid-lowering therapies during pregnancy should generally have little impact on the long-term risk associated with primary hypercholesterolaemia. Therefore, simvastatin must not be taken by women who are pregnant, planning a pregnancy or suspect they are pregnant. Treatment with simvastatin must be suspended until the end of pregnancy or until pregnancy has been conclusively ruled out (see sections 4.3 and 5.3).

Breast-feeding
It is unknown whether simvastatin or its metabolites are excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious undesirable effects affecting nursing infants, simvastatin must not be used by breast-feeding women (see section 4.3).

Fertility
No data from clinical trials on the effects of simvastatin on human fertility are available. In studies, simvastatin did not affect the fertility of rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Simvastatin has no or negligible influence on the ability to drive and use machines. However, whilst driving or using machines, it should be taken into account that dizziness has been reported rarely in post-marketing experience.

4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical trials and/or post-marketing use, have been categorised based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials such as HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). In HPS, only myalgia, increases in serum transaminases and CK level as well as serious undesirable effects were documented. In 4S, all the events listed below were reported. Incidence rates that for simvastatin were less than or similar to that of placebo in these trials and similar spontaneous reports about events with a possible causal relationship with the therapy have been categorised as "rare".

In HPS (see section 5.1), 20,536 patients received either 40 mg simvastatin/day (n = 10,269) or placebo (n = 10,267). Over the mean study duration of 5 years, the safety profiles were similar between patients treated with 40 mg simvastatin and the placebo group. Discontinuation rates due to undesirable effects were similar in both groups (4.8% in the simvastatin group vs. 5.1% in the placebo group). Myopathy occurred in less than 0.1% of patients treated with 40 mg simvastatin. Elevated transaminases (to more than three-fold the upper limit of normal, confirmed by repeat test) occurred in 0.21% (n = 21) of patients treated with 40 mg simvastatin, and 0.09% (n = 9) of patients treated with placebo.

The frequencies of the adverse events are categorised as follows:

Very common (> 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Rare: anaemia

Immune system disorders
Very rare: anaphylaxis

Psychiatric disorders
Very rare: insomnia
Not known: depression

Nervous system disorders
Rare: headache, paraesthesia, dizziness, peripheral neuropathy
Very rare: memory impairment

Eye disorders
Rare: vision blurred, visual impairment

Respiratory, thoracic and mediastinal disorders
Not known: interstitial lung disease (see section 4.4)

Gastrointestinal disorders
Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

Hepatobiliary disorders
Rare: hepatitis/jaundice
Very rare: (sometimes fatal) liver failure

Skin and subcutaneous tissue disorders
Rare: rash, pruritus, alopecia
Very rare: lichenoid drug eruptions

Musculoskeletal and connective tissue disorders
Rare: myopathy* (including myositis), rhabdomyolysis with or without acute renal failure (see section 4.4), myalgia, muscle cramps
Very rare: muscle rupture
Not known: tendinopathy, sometimes to the point of tendon rupture, immune-mediated necrotising myopathy**

* In a clinical trial, myopathy occurred commonly in patients treated with 80 mg simvastatin per day (1.0%), as compared to patients treated with 20 mg simvastatin per day (0.02%) (see sections 4.4 and 4.5).
** There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase levels that persist despite discontinuation of statin treatment. In muscle biopsies, necrotising myopathy without significant inflammation is observed. Improvement occurs when immunosuppressants are used (see section 4.4).

Reproductive system and breast disorders
Very rare: gynecomastia

Not known: erectile dysfunction

General disorders and administration site conditions
Rare: asthenia

An apparent hypersensitivity syndrome has been reported rarely, including one or more of the following symptoms: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, erythrocyte sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Investigations
Rare: elevated serum transaminases (ALT, AST, γ-GT) (see section 4.4 *Hepatic effects*), elevated alkaline phosphatase and serum CK levels (see section 4.4)

Increases in HbA1c and fasting glucose levels have been reported in association with statins, including simvastatin.

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) in association with statin use, including simvastatin. These are generally not serious and are reversible upon statin discontinuation, with variable times to onset (1 day to years) and resolution of symptoms (median of 3 weeks).

The following additional undesirable effects have been reported with some statins:

- Sleep disorders, including nightmares
- Sexual difficulties
- Diabetes mellitus: Frequency depends on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/l, BMI > 30 kg/m^2, elevated triglycerides, history of hypertension).

Paediatric population
In a 48-week study involving children and adolescents (boys: Tanner stage II and above, girls: at least 1 year post-menarche) 10-17 years of age with heterozygous familial hypercholesterolaemia (n = 175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the placebo group. Long-term effects on physical, intellectual and sexual development are unknown. No sufficient data are currently available after one year of treatment (see sections 4.2, 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

To date, a few cases of overdose have been reported. The maximum dose taken was 3.6 g simvastatin. None of the patients experienced sequelae. No specific experience regarding treatment of an overdose of simvastatin is available.
In case of an overdose, symptomatic and supportive measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors,

ATC code: C10A A01

Mechanism of action
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding beta hydroxy acid, which is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin reduces LDL cholesterol levels in case of both normal and elevated baseline levels. LDL is formed from VLDL and is catabolised predominantly by specific LDL receptors. The mechanism of the LDL-lowering effect of simvastatin is likely based on both reduction of VLDL cholesterol concentration and induction of LDL receptors, i.e. reduced production as well as increased catabolism of LDL cholesterol. Apolipoprotein B concentration also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL cholesterol and reduces plasma triglycerides. As a result of these changes, the ratios of total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol are reduced.

Clinical efficacy and safety
<u>High risk of coronary heart disease (CHD) or existing coronary heart disease</u>
In the Heart Protection Study (HPS), the effects of therapy with simvastatin were assessed in 20,536 patients (age 40-80 years) with or without hyperlipidaemia with CHD, other occlusive arterial diseases or diabetes mellitus. In this study, 10,269 patients received 40 mg simvastatin per day and 10,267 patients placebo for a mean study duration of 5 years. At the start of the study, 6,793 patients (33%) had LDL cholesterol levels below 116 mg/dl; 5,063 patients (25%) had levels between 116 mg/dl and 135 mg/dl; and 8,680 patients (42%) had levels greater than 135 mg/dl.

As compared to placebo, treatment with 40 mg simvastatin per day significantly reduced the total mortality risk (1,328 [12.9%] in patients treated with simvastatin versus 1,507 [14.7%] in patients receiving placebo; $p = 0.0003$), due to an 18% reduction in CHD mortality (587 [5.7%] versus 707 [6.9%]; $p = 0.0005$; absolute risk reduction of 1.2%). The reduction in mortality rate due to a non-cardiovascular cause was not statistically significant.
Simvastatin also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal myocardial infarction or CHD death) by 27% ($p < 0.0001$). Simvastatin reduced the need for coronary revascularisation procedures (including coronary artery bypass surgery or percutaneous transluminal coronary angioplasty) by 30% ($p < 0.0001$) and for peripheral and other non-coronary revascularisation procedures by 16% ($p = 0.006$). Simvastatin reduced the risk of stroke by 25% ($p < 0.0001$), attributable to a 30% reduction in risk of ischaemic stroke ($p < 0.0001$). In addition, within the subgroup of patients with diabetes, simvastatin reduced the risk of developing macrovascular complications including peripheral revascularisation procedures (surgery or angioplasty), lower limb amputations or leg ulcers by 21% ($p = 0.0293$). The risk reduction by simvastatin was similar in all subgroups of patients, including those without CHD but with cerebrovascular or peripheral artery disease, women and men, those aged under or over 70 years at the start of the study, presence or absence of hypertension, and notably also those with baseline LDL cholesterol under 3.0 mmol/l upon enrolment.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total cholesterol 212-309 mg/dl (5.5-8.0 mmol/l). In this multicentre, randomised, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet and standard care as well as either simvastatin 20-40 mg/day ($n = 2,221$) or placebo ($n = 2,223$) for a median treatment duration of 5.4 years. Simvastatin reduced the mortality risk by 30% (absolute risk reduction of 3.3%). The risk of CHD mortality was reduced by 42% (absolute risk reduction of 3.5%). Simvastatin also decreased the risk of major coronary events (CHD mortality plus hospital-verified and silent non-fatal MI) by 34%. Furthermore, simvastatin reduced the risk of fatal or non-fatal cerebrovascular events (stroke and transient ischaemic attacks) by 28%. There was no statistically significant difference between the two groups in non-cardiovascular mortality.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with 80 mg simvastatin versus 20 mg simvastatin (median follow-up 6.7 years) on major vascular events (MVEs; defined as fatal CHD, non-fatal myocardial infarction, coronary revascularisation procedures, non-fatal or fatal stroke, peripheral revascularisation procedures) in 12,064 patients with a history of myocardial infarction. There was no significant difference regarding these events between the two groups: 20 mg simvastatin (n = 1,553; 25.7%) vs. 80 mg simvastatin (n = 1,477; 24.5%); RR 0.94, 95% CI: 0.88-1.01. The absolute difference in LDL cholesterol between the two groups over the course of the study was 0.35 ± 0.01 mmol/l. The safety profiles were also similar between the two treatment groups, except that the incidence of myopathy was approximately 1.0% for patients on 80 mg simvastatin compared with 0.02% for patients on 20 mg simvastatin. 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%.

Primary hypercholesterolaemia and combined hypercholesterolaemia
In comparison studies on the efficacy and safety of treatment with simvastatin in patients with hypercholesterolemia, treatment with 10 mg, 20 mg, 40 mg and 80 mg simvastatin daily on average reduced LDL cholesterol by 30%, 38%, 41% and 47%, respectively. In studies on mixed hypercholesterolaemia, treatment with 40 mg and 80 mg simvastatin resulted in mean reductions in triglycerides of 28% and 33% (placebo: 2%), respectively, and mean increases in HDL cholesterol of 13% and 16% (placebo: 3%), respectively.

Paediatric population
In a double-blind, placebo-controlled trial, 175 patients (99 boys: Tanner stage II and above, 76 girls: at least 1 year post-menarche) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (HeFH) were randomised to receive either simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL cholesterol level between 160 mg/dl and 400 mg/dl and at least one parent with an LDL cholesterol level > 189 mg/dl. The simvastatin dose (single daily dose in the evening) was 10 mg for the first 8 weeks, 20 mg for the following 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients were selected to continue therapy. They received 40 mg simvastatin or placebo.

Simvastatin significantly decreased plasma levels of LDL cholesterol, triglycerides and apo B. Results from the extension study after 48 weeks were similar to those of the base study. After 24 weeks of treatment, the mean LDL cholesterol level was 124.9 mg/dl (range: 64.0-289.0 mg/dl) in the group receiving 40 mg simvastatin, as compared to 207.8 mg/dl (range: 128.0-334.0 mg/dl) in the placebo group.

After 24 weeks of simvastatin treatment (with doses increasing from 10, 20 and 40 mg per day at 8-week intervals), simvastatin decreased the mean LDL cholesterol level by 36.8% (placebo: 1.1% increase from baseline), apo B by 32.4% (placebo: 0.5%), and median triglyceride levels by 7.9% (placebo: 3.2%) and increased mean HDL cholesterol levels by 8.3% (placebo: 3.6%). The long-term benefits of simvastatin on cardiovascular events in children with HeFH are unknown.

The safety and efficacy of doses over 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. There are no data on the long-term effect of simvastatin therapy in childhood on a reduction in morbidity and mortality in adulthood available, either.

5.2 Pharmacokinetic properties

Simvastatin, which is an inactive lactone, is readily hydrolysed *in vivo* to the corresponding beta hydroxy acid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

Absorption
In humans, simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta hydroxy acid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after ingestion. Concomitant food intake did not affect absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution
Plasma protein binding of simvastatin and its active metabolite in humans is > 95%.

Elimination
Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are beta hydroxy acid and four additional active metabolites. Following an oral dose of radioactively labelled simvastatin in healthy volunteers, 13% of the radioactivity was recovered in the urine and 60% in the faeces within 96 hours. The latter amount represents absorbed fractions excreted in bile as well as unabsorbed substance. Following intravenous injection of the beta hydroxy acid metabolite, its half-life averaged approx. 1.9 hours. An average of only 0.3% of the IV dose was excreted in urine as inhibitors.

Simvastatin acid is taken up actively into the hepatocytes by the transporter OATP1B1. Simvastatin is a substrate of the BCRP efflux transporter.

Special populations
SLCO1B1 polymorphism
Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean bioavailability (AUC) of the main active metabolite, simvastatin acid, is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The incidence of the C allele in the European population is 18%. In patients with SLCO1B1 polymorphism, there is a risk of increased exposure to simvastatin acid, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

5.3 Preclinical safety data

Based on conventional animal studies of pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient that may be expected on account of the pharmacological mechanism. At maximally tolerated doses in rats and rabbits, simvastatin produced no foetal malformations, and had no effects on fertility, reproduction or neonatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxyanisole
Lactose monohydrate
Pregelatinised maize starch
Ascorbic acid
Citric acid monohydrate
Microcrystalline cellulose
Croscarmellose sodium

Magnesium stearate [vegetable]
Hydroxypropylcellulose
Hypromellose
Titanium dioxide
Talc
Iron oxide yellow
Iron oxide red
Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters
Pack size: 30 film-coated tablets

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBERS IN GERMANY

Not applicable.

9. DATE OF FIRST AUTHORISATION IN GERMANY

Not applicable.

10. DATE OF REVISION OF THE TEXT

02/2020

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.