PRODUCT INFORMATION

# ZEKLEN®

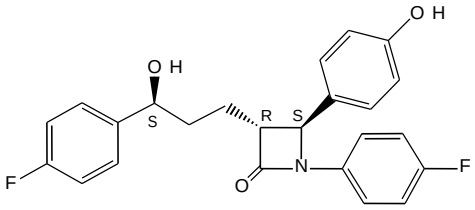
(ezetimibe and simvastatin)

## NAME OF THE MEDICINE

***Ezetimibe***

The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4. The CAS registry number for Ezetimibe is CAS-163222-33-1.

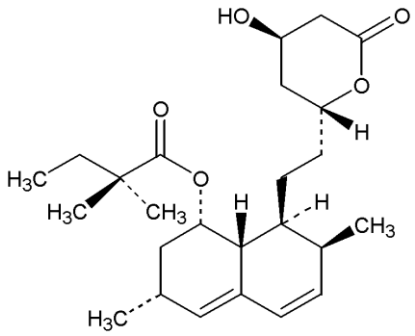
Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:




***Simvastatin***

Simvastatin, an inactive lactone, is hydrolysed to the corresponding β-hydroxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. The CAS registry number for simvastatin is CAS–79902-63-9.

Simvastatin is a white to off-white, non-hygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Its structural formula is:



## DESCRIPTION

ZEKLEN (ezetimibe/simvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

ZEKLEN is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (ZEKLEN 10/10), 20 mg of simvastatin (ZEKLEN 10/20), 40 mg of simvastatin (ZEKLEN 10/40), or 80 mg of simvastatin (ZEKLEN 10/80).

Each tablet contains the following inactive ingredients: butylated hydroxyanisole, citric acid monohydrate, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and propyl gallate.

## PHARMACOLOGY

### Mechanism of Action

***ZEKLEN***
Plasma cholesterol homeostasis depends on the balance between intestinal absorption and endogenous synthesis. ZEKLEN contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. ZEKLEN reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

***Ezetimibe***
Ezetimibe inhibits the intestinal absorption of cholesterol. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction.

In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [$^{14}$C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.

***Simvastatin***
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active β-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.

**Pharmacokinetics**
***Ezetimibe***
*Absorption*
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations ($C_{max}$) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10-mg tablets.

*Distribution*
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

*Metabolism*
Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

*Excretion*
Following oral administration of $^{14}$C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

***Simvastatin***

*Absorption*

The availability of the β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the β-hydroxyacid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.

*Distribution*

Both simvastatin and the β-hydroxyacid are bound to human plasma proteins (95%).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.

*Metabolism*

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

In man, 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 its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the systemic circulation is low.

Following an intravenous injection of the β-hydroxyacid metabolite, its half-life averaged 1.9 hours.

In dose proportionality studies utilising doses of simvastatin of 5 mg, 10 mg, 20 mg, 60 mg, 90 mg and 120 mg there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose.

*Excretion*

Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. The amount recovered in the faeces represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Following an intravenous injection of the β-hydroxyacid metabolite an average of only 0.3% of the IV dose was excreted in urine as inhibitors.

**Characteristics in Special Populations**

**Paediatric Patients**

***Ezetimibe***

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population <10 years of age are not available.

***Simvastatin***
The pharmacokinetics of simvastatin has not been studied in the paediatric population.

**Elderly Patients**
***Ezetimibe***
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe (see **PRECAUTIONS**).

**Hepatic Insufficiency**
***Ezetimibe***
After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic insufficiency, ezetimibe is not recommended in these patients (see **PRECAUTIONS**).

**Renal Insufficiency**
***Ezetimibe***
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 mL/min/1.73 $m^2$), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

***Simvastatin***
In a study of patients with severe renal insufficiency (creatinine clearance < 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

***Gender***
Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

***Race***
Based on a meta-analysis of pharmacokinetic studies with ezetimibe, there were no pharmacokinetic differences between Blacks and Caucasians.

## CLINICAL TRIALS

Five multicentre, double-blind studies conducted with ZEKLEN in patients with primary hypercholesterolaemia are reported: two were comparisons with simvastatin and two were comparisons with atorvastatin and one was a comparison with rosuvastatin.

In controlled clinical studies, ZEKLEN significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

No incremental benefit of ZEKLEN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been demonstrated.

### *Primary Hypercholesterolaemia*

*ZEKLEN*

In a multicentre, double-blind, placebo-controlled, 12-week trial, 887 hypercholesterolaemic patients were randomised to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or co-administered ezetimibe and simvastatin equivalent to ZEKLEN (10/10, 10/20, 10/40, and 10/80). ZEKLEN significantly lowered total-C, LDL-C, Apo B, TG, non-HDL-C, and C-reactive protein compared to all doses of simvastatin. The effects of ZEKLEN on HDL-C were similar to the effects seen with simvastatin. Further analysis showed ZEKLEN significantly increased HDL-C compared with placebo. (See Tables 1 [mean absolute change] and 1a [mean percent change].)

## Table 1
## Response to ZEKLEN in Patients with Primary Hypercholesterolaemia (Mean[a] Absolute Change from Untreated Baseline[b])

| Treatment (Daily Dose) | N | Total-C Abs† [Baseline] | LDL-C Abs† [Baseline] | Apo B Abs† [Baseline] | HDL-C Abs† [Baseline] | TG[a] Abs† [Baseline] | Non-HDL-C Abs† [Baseline] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ZEKLEN doses) | 353 | -2.55 [6.73] | -2.42 [4.52] | -0.68 [1.60] | +0.10 [1.31] | -0.48 [1.90] | -2.65 [5.42] |
| Pooled data (All simvastatin doses) | 349 | -1.78 [6.70] | -1.75 [4.52] | -0.47 [1.59] | +0.09 [1.28] | -0.26 [1.89] | -1.87 [5.42] |
| Ezetimibe10 mg | 92 | -0.94 [6.79] | -0.91 [4.55] | -0.23 [1.58] | +0.08 [1.32] | -0.21 [1.85] | -1.02 [5.46] |
| Placebo | 93 | +0.13 [6.66] | +0.11 [4.49] | +0.04 [1.59] | +0.02 [1.30] | -0.03 [1.83] | +0.11 [5.36] |
| ZEKLEN by dose | | | | | | | |
| 10/10 | 87 | -2.13 [6.70] | -2.09 [4.49] | -0.59 [1.62] | +0.11 [1.31] | -0.39 [1.87] | -2.24 [5.39] |
| 10/20 | 86 | -2.52 [6.88] | -2.35 [4.63] | -0.69 [1.63] | +0.09 [1.33] | -0.53 [2.00] | -2.62 [5.55] |
| 10/40 | 89 | -2.69 [6.71] | -2.47 [4.45] | -0.72 [1.60] | +0.10 [1.31] | -0.56 [1.93] | -2.79 [5.40] |
| 10/80 | 91 | -2.88 [6.64] | -2.76 [4.50] | -0.74 [1.57] | +0.08 [1.29] | -0.46 [1.81] | -2.95 [5.35] |
| Simvastatin by dose | | | | | | | |
| 10 mg | 81 | -1.41 [6.69] | -1.44 [4.53] | -0.38 [1.59] | +0.05 [1.30] | -0.8 [1.82] | -1.47 [5.39] |
| 20 mg | 90 | -1.61 [6.66] | -1.58 [4.49] | -0.41 [1.58] | +0.07 [1.29] | -0.25 [1.85] | -1.68 [5.38] |
| 40 mg | 91 | -1.95 [6.71] | -1.90 [4.55] | -0.55 [1.61] | +0.10 [1.25] | -0.33 [1.90] | -2.04 [5.47] |
| 80 mg | 87 | -2.16 [6.72] | -2.09 [4.52] | -0.57 [1.59] | +0.13 [1.28] | -0.43 [1.94] | -2.29 [5.44] |

† Mean absolute change from baseline (units are mmol/L for all parameters except Apo B, which is in g/L)
[a] For triglycerides, median absolute change from baseline
[b] Baseline - on no lipid-lowering drug

## Table 1a
## Response to ZEKLEN in Patients with Primary Hypercholesterolaemia
## (Mean[a] Percent Change from Untreated Baseline[b])

| Treatment (Daily Dose) | N | Total-C Pct† [Baseline‡] | LDL-C Pct† [Baseline‡] | Apo B Pct† [Baseline‡] | HDL-C Pct† [Baseline‡] | TG[a] Pct† [Baseline‡] | Non-HDL-C Pct† [Baseline‡] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ZEKLEN doses)[c] | 353 | -38 [6.73] | -53 [4.52] | -42 [1.60] | +8 [1.31] | -28 [1.90] | -49 [5.42] |
| Pooled data (All simvastatin doses)[c] | 349 | -26 [6.70] | -38 [4.52] | -29 [1.59] | +8 [1.28] | -15 [1.89] | -34 [5.42] |
| Ezetimibe10 mg | 92 | -14 [6.79] | -20 [4.55] | -15 [1.58] | +7 [1.32] | -13 [1.85] | -19 [5.46] |
| Placebo | 93 | +2 [6.66] | +3 [4.49] | +3 [1.59] | +2 [1.30] | -2 [1.83] | +2 [5.36] |
| ZEKLEN by dose | | | | | | | |
| 10/10 | 87 | -32 [6.70] | -46 [4.49] | -36 [1.62] | +9 [1.31] | -21 [1.87] | -41 [5.39] |
| 10/20 | 86 | -37 [6.88] | -51 [4.63] | -41 [1.63] | +8 [1.33] | -31 [2.00] | -47 [5.55] |
| 10/40 | 89 | -39 [6.71] | -55 [4.45] | -44 [1.60] | +9 [1.31] | -32 [1.93] | -51 [5.40] |
| 10/80 | 91 | -43 [6.64] | -61 [4.50] | -47 [1.57] | +6 [1.29] | -28 [1.81] | -55 [5.35] |
| Simvastatin by dose | | | | | | | |
| 10 mg | 81 | -21 [6.69] | -31 [4.53] | -23 [1.59] | +5 [1.30] | -4 [1.82] | -27 [5.39] |
| 20 mg | 90 | -24 [6.66] | -35 [4.49] | -25 [1.58] | +6 [1.29] | -14 [1.85] | -31 [5.38] |
| 40 mg | 91 | -29 [6.71] | -42 [4.55] | -33 [1.61] | +8 [1.25] | -19 [1.90] | -37 [5.47] |
| 80 mg | 87 | -32 [6.72] | -46 [4.52] | -35 [1.59] | +11 [1.28] | -26 [1.94] | -41 [5.44] |

† Mean percent change from baseline
‡ Baseline units are mmol/L for all parameters except Apo B, which is in g/L

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZEKLEN doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin, and significantly increased HDL-C compared to placebo.

In a similarly designed study, results for all lipid parameters were generally consistent. In a pooled analysis of these two studies, the incremental reduction of LDL-C concentration with the combination tablet was generally consistent across subgroups tested, including risk factor status, age, and baseline lipid profile. In addition, the lipid response to ZEKLEN was similar in patients with TG levels greater than or less than 2.3mmol/L (200 mg/dL).

In a multicentre, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥ 3.4 mmol/L (130 mg/dL) were randomised to one of four treatment groups: co-administered ezetimibe and simvastatin equivalent to ZEKLEN (10/10, 10/20, and 10/40), or simvastatin 20 mg. Patients not reaching an LDL-C < 2.6 mmol/L (100 mg/dL) had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg. At Week 5, the LDL-C reductions with ZEKLEN 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg. In addition, at Week 5, significantly more patients receiving ZEKLEN 10/10, 10/20, or 10/40 attained LDL-C target compared to those receiving simvastatin 20 mg (see Tables 2 [mean absolute change] and 2a [mean percent change]). Week 5 results for LDL-C reduction and percentage attaining LDL-C target were consistent with the end of study results (Week 23).

**Table 2**
**Response to ZEKLEN after 5 Weeks in Patients with CHD or CHD Risk Equivalents and an LDL-C ≥ 3.4 mmol/L (130 mg/dL)**
**(Mean Absolute Change from Untreated Baseline)**

| | Simvastatin 20 mg [Baseline] | ZEKLEN 10/10 [Baseline] | ZEKLEN 10/20 [Baseline] | ZEKLEN 10/40 [Baseline] |
|---|---|---|---|---|
| N | 253 | 251 | 109 | 97 |
| LDL-C Abs[a] | -1.6 [4.49] | -2.0 [4.26] | -2.3 [4.33] | -2.6 [4.41] |
| Percent attaining LDL-C goal | 46 | 75 | 83 | 88 |

[a] Mean absolute change from untreated baseline, expressed as mmol/L

**Table 2a**
**Response to ZEKLEN after 5 Weeks in Patients with CHD or CHD Risk Equivalents and an LDL-C ≥ 3.4 mmol/L (130 mg/dL)**
**(Mean Percent Change from Untreated Baseline)**

| | Simvastatin 20 mg [Baseline†] | ZEKLEN 10/10 [Baseline†] | ZEKLEN 10/20 [Baseline†] | ZEKLEN 10/40 [Baseline†] |
|---|---|---|---|---|
| N | 253 | 251 | 109 | 97 |
| LDL-C Pct[a] | -38 [4.49] | -47 [4.26] | -53 [4.33] | -59 [4.41] |
| Percent attaining LDL-C goal | 46 | 75 | 83 | 88 |

† Baseline values expressed as mmol/L
[a] Mean percent change from untreated baseline

In a multicentre, double-blind, 6-week study, 1902 patients with primary hypercholesterolaemia, who had not met their NCEP ATP III target LDL-C goal, were randomised to one of eight treatment groups: ZEKLEN (10/10, 10/20, 10/40 or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg or 80 mg). When patients receiving all doses of ZEKLEN were compared to those receiving all doses of atorvastatin, ZEKLEN lowered total-C, LDL-C, ApoB and non-HDL-C, and increased HDL-C significantly more than atorvastatin. The effects of ZEKLEN on TG were similar to the effects seen with atorvastatin (see Tables 3 [mean absolute change] and 3a [mean percent change]).

**Table 3**
**Response to ZEKLEN and Atorvastatin in Patients with Primary Hypercholesterolaemia (Mean[a] Absolute Change from Untreated Baseline[b])**

| Treatment (Daily Dose) | N | Total-C Abs† [Baseline] | LDL-C Abs† [Baseline] | Apo B Abs† [Baseline] | HDL-C Abs† [Baseline] | TG[a] Abs† [Baseline] | Non-HDL-C Abs† [Baseline] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ZEKLEN doses) | 951 | -2.64 [6.83] | -2.46 [4.60] | -0.71 [1.65] | +0.09 [1.27] | -0.51 [1.93] | -2.73 [5.56] |
| Pooled data (All atorvastatin doses) | 951 | -2.32 [6.84] | -2.11 [4.63] | -0.63 [1.65] | +0.04 [1.26] | -0.45 [1.89] | -2.36 [5.58] |
| ZEKLEN by dose | | | | | | | |
| 10/10 | 238 | -2.33 [6.83] | -2.17 [4.57] | -0.62 [1.65] | +0.09 [1.27] | -0.44 [1.96] | -2.41 [5.56] |
| 10/20 | 238 | -2.52 [6.84] | -2.36 [4.62] | -0.67 [1.64] | +0.08 [1.27] | -0.42 [1.89] | -2.60 [5.57] |
| 10/40 | 238 | -2.81 [6.85] | -2.64 [4.60] | -0.77 [1.66] | +0.10 [1.27] | -0.55 [1.94] | -2.91 [5.58] |
| 10/80 | 237 | -2.90 [6.81] | -2.68 [4.59] | -0.80 [1.65] | +0.08 [1.27] | -0.60 [1.92] | -2.98 [5.54] |
| Atorvastatin by dose | | | | | | | |
| 10 mg | 238 | -1.82 [6.77] | -1.67 [4.53] | -0.51 [1.63] | +0.07 [1.25] | -0.41 [1.93] | -1.89 [5.52] |
| 20 mg | 237 | -2.23 [6.86] | -2.03 [4.61] | -0.61 [1.67] | +0.05 [1.26] | -0.46 [1.96] | -2.28 [5.60] |
| 40 mg | 237 | -2.46 [6.85] | -2.25 [4.65] | -0.67 [1.64] | +0.04 [1.30] | -0.41 [1.82] | -2.49 [5.55] |
| 80 mg | 239 | | | | | | -2.78 |

| | | | | | |
|---|---|---|---|---|---|
| | [6.89] | | | | |
| | -2.49 [4.72] | -0.74 [1.67] | +0.10 [1.24] | -0.59 [1.87] | -2.79 [5.65] |

† Mean absolute change from baseline (units are mmol/L for all parameters except Apo B, which is in g/L)
[a] For triglycerides, median absolute change from baseline
[b] Baseline - on no lipid-lowering drug

**Table 3a**
**Response to ZEKLEN and Atorvastatin in Patients with Primary Hypercholesterolaemia (Mean[a] Percent Change from Untreated Baseline[b])**

| Treatment (Daily Dose) | N | Total-C Pct† [Baseline‡] | LDL-C Pct† [Baseline‡] | Apo B Pct† [Baseline‡] | HDL-C Pct† [Baseline‡] | TG[a] Pct† [Baseline‡] | Non-HDL-C Pct† [Baseline‡] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ZEKLEN doses) | 951 | -38[c] [6.83] | -53[c] [4.60] | -43[c] [1.65] | +8[c] [1.27] | -27 [1.93] | -49[c] [5.56] |
| Pooled data (All atorvastatin doses) | 951 | -34 [6.84] | -45 [4.63] | -38 [1.65] | +4 [1.26] | -26 [1.89] | -42 [5.58] |
| ZEKLEN by dose | | | | | | | |
| 10/10 | 238 | -34[d] [6.83] | -47[d] [4.57] | -37[d] [1.65] | +8 [1.27] | -26 [1.96] | -43[d] [5.56] |
| 10/20 | 238 | -37[d] [6.84] | -51[d] [4.62] | -40[d] [1.64] | +7 [1.27] | -25 [1.89] | -46[d] [5.57] |
| 10/40 | 238 | -41[d] [6.85] | -57[d] [4.60 | -46[d] [1.66] | +9[d] [1.27] | -27 [1.94] | -52[d] [5.58] |
| 10/80 | 237 | -43[d] [6.81] | -59[d] [4.59] | -48[d] [1.65] | +8[d] [1.27] | -31 [1.92] | -54[d] [5.54] |
| Atorvastatin by dose | | | | | | | |
| 10 mg | 238 | -27 [6.77] | -36 [4.53] | -31 [1.63] | +7 [1.25] | -21 [1.93] | -34 [5.52] |
| 20 mg | 237 | -32 [6.86] | -44 [4.61] | -37 [1.67] | +5 [1.26] | -25 [1.96] | -41 [5.60] |
| 40 mg | 237 | -36 [6.85] | -48 [4.65] | -40 [1.64] | +4 [1.30] | -24 [1.82] | -45 [5.55] |
| 80 mg | 239 | -40 [6.89] | -53 [4.72] | -44 [1.67] | +1 [1.24] | -32 [1.87] | -50 [5.65] |

† Mean percent change from baseline
‡ Baseline units are mmol/L for all parameters except Apo B, which is in g/L
[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with atorvastatin
[d] p<0.05 for difference with atorvastatin at equal mg doses of the simvastatin component

In a multicentre, double-blind, 24-week, forced titration study, 788 patients with primary hypercholesterolaemia, who had not met their NCEP ATP III target LDL-C goal, were randomised to receive co-administered ezetimibe and simvastatin equivalent to ZEKLEN (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, ZEKLEN lowered LDL-C to a greater degree than atorvastatin (see Tables 4 [mean absolute change] and 4a [mean percent change]).

## Table 4
## Response to ZEKLEN and Atorvastatin in Patients with Primary Hypercholesterolemia
## (Mean[a] Absolute Change from Untreated Baseline[b])

| Treatment | N | Total C Abs🗁 [Baseline] | LDL-C Abs🗁 [Baseline] | Apo B Abs🗁 [Baseline] | HDL-C Abs🗁 [Baseline] | TG[a] Abs🗁 | Non-HDL-C Abs🗁 [Baseline] |
|---|---|---|---|---|---|---|---|
| Week 6 | | | | | | | |
| Atorvastatin 10 mg[c] | 262 | -1.95 [6.90] | -1.75 [4.67] | -0.54 [1.70] | +0.05 [1.21] | -0.42 [1.94] | -2.00 [5.68] |
| ZEKLEN 10/10[d] | 263 | -2.34 [6.87] | -2.15 [4.65] | -0.65 [1.72] | +0.08 [1.21] | -0.52 [1.97] | -2.42 [5.66] |
| ZEKLEN 10/20[e] | 263 | -2.48 [6.83] | -2.33 [4.63] | -0.70 [1.69] | +0.11 [1.21] | -0.46 [1.99] | -2.59 [5.62] |
| Week 12 | | | | | | | |
| Atorvastatin 20 mg | 246 | -2.29 [6.89] | -2.06 [4.66] | -0.64 [1.69] | +0.07 [1.20] | -0.52 [1.95] | -2.36 [5.68] |
| ZEKLEN 10/20 | 250 | -2.52 [6.86] | -2.35 [4.65] | -0.07 [1.71] | +0.10 [1.21] | -0.52 [1.95] | -2.62 [5.65] |
| ZEKLEN 10/40 | 252 | -2.69 [6.83] | -2.52 [4.64] | -0.76 [1.69] | +0.14 [1.21] | -0.54 [1.98] | -2.83 [5.62] |
| Week 18 | | | | | | | |
| Atorvastatin 40 mg | 237 | -2.56 [6.88] | -2.28 [4.64] | -0.72 [1.69] | +0.08 [1.21] | -0.59 [1.95] | -2.64 [5.67] |
| ZEKLEN 10/40[f] | 482 | -2.78 [6.84] | -2.58 [4.64] | -0.77 [1.70] | +0.12 [1.21] | -0.60 [1.97] | -2.90 [5.63] |
| Week 24 | | | | | | | |
| Atorvastatin 80 mg | 228 | -2.79 [6.88] | -2.45 [4.64] | -0.76 [1.69] | +0.07 [1.21] | -0.66 [1.95] | -2.85 [5.68] |
| ZEKLEN 10/80[f] | 459 | -2.97 [6.84] | -2.75 [4.64] | -0.83 [1.70] | +0.14 [1.21] | -0.68 [1.97] | -3.11 [5.63] |

🗁 Mean absolute change from baseline (units are mmol/L for all parameters except Apo B, which is in g/L)

[a] For triglycerides, median absolute change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24
[d] ZEKLEN 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[e] ZEKLEN 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[f] Data pooled for common doses of ZEKLEN at Weeks 18 and 24.

**Table 4a**
**Response to ZEKLEN and Atorvastatin in Patients with Primary Hypercholesterolemia**
**(Mean[a] Percent Change from Untreated Baseline[b])**

| Treatment | N | Total C Pct▱ [Baseline‡] | LDL-C Pct▱ [Baseline‡] | Apo B Pct▱ [Baseline‡] | HDL-C Pct▱ [Baseline‡] | TG[a] Pct▱ | Non-HDL-C Pct▱ [Baseline‡] |
|---|---|---|---|---|---|---|---|
| Week 6 | | | | | | | |
| Atorvastatin 10 mg[c] | 262 | -28 [6.90] | -37 [4.67] | -32 [1.70] | +5 [1.21] | -23 [1.94] | -35 [5.68] |
| ZEKLEN 10/10[d] | 263 | -34[f] [6.87] | -46[f] [4.65] | -38[f] [1.72] | +8[f] [1.21] | -26 [1.97] | --43[f] [5.66] |
| ZEKLEN 10/20[e] | 263 | -36[f] [6.83] | -50[f] [4.63] | -41[f] [1.69] | +10[f] [1.21] | -25 [1.99] | -46[f] [5.62] |
| Week 12 | | | | | | | |
| Atorvastatin 20 mg | 246 | -33 [6.89] | -44 [4.66] | -38 [1.69] | +7 [1.20] | -28 [1.95] | -42 [5.68] |
| ZEKLEN 10/20 | 250 | -37[f] [6.86] | -50[f] [4.65] | -41[f] [1.71] | +9 [1.21] | -28 [1.95] | -46[f] [5.65] |
| ZEKLEN 10/40 | 252 | -39[f] [6.83] | -54[f] [4.64] | -45[f] [1.69] | +12[f] [1.21] | -31 [1.98] | -50[f] [5.62] |
| Week 18 | | | | | | | |
| Atorvastatin 40 mg | 237 | -37 [6.88] | --49 [4.64] | -42 [1.69] | +8 [1.21] | -31 [1.95] | -47 [5.67] |
| ZEKLEN 10/40[g] | 482 | -40[f] [6.84] | -56[f] [4.64] | -45[f] [1.70] | +11[f] [1.21] | -32 [1.97] | -52[f] [5.63] |
| Week 24 | | | | | | | |
| Atorvastatin 80 mg | 228 | -40 [6.88] | -53 [4.64] | -45 [1.69] | +6 [1.21] | -35 [1.95] | -50 [5.68] |
| ZEKLEN 10/80[g] | 459 | -43[f] [6.84] | --59[f] [4.64] | -49[f] [1.70] | +12[f] [1.21] | -35 [1.97] | -55[f] [5.63] |

▱ Mean percent change from baseline
‡ Baseline values expressed as mmol/L except Apo B, which is in g/L
[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24
[d] ZEKLEN 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[e] ZEKLEN 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
[f] $p \leq 0.05$ for difference with atorvastatin in the specified week
[g] Data pooled for common doses of ZEKLEN at Weeks 18 and 24.

In a multicentre, double-blind, 6-week study, 2959 patients with hypercholesterolaemia, who had not met their NCEP ATP III target LDL-C goal, were randomised to one of six treatment groups: ZEKLEN (10/20, 10/40 or 10/80) or rosuvastatin (10 mg, 20 mg or 40 mg). When patients receiving all doses of ZEKLEN were compared to those receiving all doses of rosuvastatin, ZEKLEN lowered total-C, LDL-C, Apo B and non-HDL-C significantly more than rosuvastatin. The effects of ZEKLEN on HDL-C were similar to the effects seen with rosuvastatin (see Tables 5 [mean absolute change] and 5a [mean percent change]).

## Table 5
## Response to ZEKLEN and Rosuvastatin in Patients with Primary Hypercholesterolaemia
## Modified-Intention-To-Treat Approach
## (Mean[a] Absolute Change from Untreated Baseline[b])

| Treatment (Daily Dose) | N | Total-C Abs▱ [Baseline‡] | LDL-C Abs▱ [Baseline‡] | Apo B Abs▱ [Baseline‡] | HDL-C Abs▱ [Baseline‡] | TG[a] Abs▱ [Baseline‡] | Non-HDL-C Abs▱ [Baseline‡] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ZEKLEN doses) | 1427 | -2.71[c] [6.65] | -2.55[c] [4.47] | -0.73[c] [1.58] | +0.09 [1.30] | -0.42 [1.77] | -2.80[c] [5.35] |
| Pooled data (All rosuvastatin doses) | 1428 | -2.50 [6.66] | -2.37 [4.48] | -0.69 [1.59] | +0.09 [1.29] | -0.42 [1.80] | -2.59 [5.36] |
| ZEKLEN by dose | | | | | | | |
| 10/20 | 476 | -2.47[d] [6.62] | -2.35[d] [4.46] | -0.67[d] [1.58] | +0.08 [1.31] | -0.35 [1.70] | -2.55[d] [5.32] |
| 10/40 | 477 | -2.68[e] [6.69] | -2.52[e] [4.48] | -0.73[e] [1.59] | +0.10 [1.30] | -0.45 [1.85] | -2.78[e] [5.38] |
| 10/80 | 474 | -2.97[f] [6.63] | -2.78[f] [4.47] | -0.80[f] [1.58] | +0.09 [1.30] | -0.50[f] [1.76] | -3.06[f] [5.34] |
| Rosuvastatin by dose | | | | | | | |
| 10 mg | 475 | -2.21 [6.65] | -2.11 [4.45] | -0.61 [1.58] | +0.08 [1.31] | -0.33 [1.83] | -2.29 [5.34 |
| 20 mg | 478 | -2.53 [6.66] | -2.39 [4.48] | -0.70 [1.59] | +0.10 [1.29] | -0.44 [1.80] | -2.63 [5.37] |
| 40 mg | 475 | -2.75 [6.66] | -2.61 [4.50] | -0.76 [1.59] | +0.10 [1.29] | -0.46 [1.75] | -2.85 [5.37] |

▱ Mean absolute change from baseline
‡ Baseline values expressed as mmol/L except Apo B, which is in g/L
[a] For triglycerides, median absolute change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with rosuvastatin
[d] p<0.05 vs. rosuvastatin 10 mg
[e] p<0.05 vs. rosuvastatin 20 mg
[f] p<0.05 vs. rosuvastatin 40 mg

**Table 5a**
**Response to ZEKLEN and Rosuvastatin in Patients with Primary Hypercholesterolaemia**
**Modified-Intention-To-Treat Approach**
**(Mean[a] % Change from Untreated Baseline[b])**

| Treatment (Daily Dose) | N | Total-C Pct [Baseline‡] | LDL-C Pct [Baseline‡] | Apo B Pct [Baseline‡] | HDL-C Pct [Baseline‡] | TG[a] Pct [Baseline‡] | Non-HDL-C Pct [Baseline‡] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ZEKLEN doses) | 1427 | -40[c] [6.65] | -56[c] [4.47] | -45[c] [1.58] | +8 [1.30] | -26 [1.77] | -51[c] [5.35] |
| Pooled data (All rosuvastatin doses) | 1428 | -37 [6.66] | -52 [4.48] | -42 [1.59] | +8 [1.29] | -25 [1.80] | -47 [5.36] |
| ZEKLEN by dose | | [d] | [d] | [d] | | [d] | [d] |
| 10/20 | 476 | -37 [6.62] | -52 [4.46] | -42 [1.58] | +7 [1.31] | -23 [1.70] | -47 [5.32] |
| 10/40 | 477 | -39[e] [6.69] | -55[e] [4.48] | -44[e] [1.59] | +8 [1.30] | -27 [1.85] | -50[e] [5.38] |
| 10/80 | 474 | -44[f] [6.63] | -61[f] [4.47] | -50[f] [1.58] | +8 [1.30] | -30[f] [1.76] | -56[f] [5.34] |
| Rosuvastatin by dose | | | | | | | |
| 10 mg | 475 | -32 [6.65] | -46 [4.45] | -37 [1.58] | +7 [1.31] | -20 [1.83] | -42 [5.34] |
| 20 mg | 478 | -37 [6.66] | -52 [4.48] | -43 [1.59] | +8 [1.29] | -26 [1.80] | -48 [5.37] |
| 40 mg | 475 | -41 [6.66] | -57 [4.50] | -47 [1.59] | +8 [1.29] | -28 [1.75] | -52 [5.37] |

▱ Mean percent change from baseline
‡ Baseline values expressed as mmol/L except Apo B, which is in g/L
[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with rosuvastatin
[d] p<0.05 vs. rosuvastatin 10 mg
[e] p<0.05 vs. rosuvastatin 20 mg
[f] p<0.05 vs. rosuvastatin 40 mg

In a double-blind, placebo-controlled, 8-week study, 240 patients with hypercholesterolaemia already receiving simvastatin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/L [100 to 160 mg/dL], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going simvastatin therapy. Among simvastatin-treated patients not at LDL-C goal at baseline (~80%), significantly more patients randomised to ezetimibe co-administered with simvastatin achieved their LDL-C goal at study endpoint compared to patients randomised to placebo co-administered with simvastatin, 76% and 21.5%, respectively. The additional corresponding LDL-C reductions for ezetimibe or placebo co-administered with simvastatin were also significantly different (27% or 3%, respectively). In addition, ezetimibe co-administered with simvastatin significantly decreased total-C, Apo B, and TG compared with placebo co-administered with simvastatin.

In a multicentre, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks with a mean LDL-C of 2.4 mmol/L (93 mg/dL), were randomised to receive either simvastatin 40 mg or the co-administered active ingredients equivalent to ZEKLEN 10/20.

ZEKLEN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg in further reducing LDL-C (-21% and 0%, respectively), total-C (-14% and -1%, respectively), Apo B (-14% and -2%, respectively), and non-HDL-C (-20% and -2%, respectively) beyond the reductions observed with simvastatin 20 mg. Results for HDL-C and TG between the two treatment groups were not significantly different. Results were not affected by type of thiazolidinedione treatment.

***ENHANCE Study***

This randomised, double-blind trial recruited 720 patients with heterozygous familial hypercholesterolaemia. The primary variable was the mean change in carotid intima media thickness (cIMT) from baseline to endpoint. Patients were treated with either simvastatin alone, 80 mg simvastatin daily or ezetimibe 10 mg in combination with simvastatin 80 mg once daily for up to two years. The mean cIMT increased by 0.0058mm following simvastatin and 0.0111mm following combined therapy with ezetimibe and simvastatin. The difference between treatments was not statistically significant – p-value 0.29 based on ANCOVA model. The reason for the lack of difference between treatment groups in the change in cIMT is unknown.

The combination had a significantly greater effect on lipid parameters compared with simvastatin alone. Mean LDL-cholesterol decreased by 56% following ezetimibe/simvastatin compared with 39% reduction following simvastatin alone ($p < 0.01$, based on ANOVA model). There were statistically greater reductions in total-C, Apo B, TG, campesterol and sitosterol following ezetimibe/simvastatin. Clinical outcome was not an objective of the ENHANCE trial.

***Clinical Studies in Paediatric (10 to 17 Years of Age) Patients***

In a multicentre, double-blind, controlled study, 142 boys and 106 post-menarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% Multiracial) with heterozygous familial hypercholesterolaemia (HeFH) were randomised to receive either co-administered ezetimibe and simvastatin equivalent to ZEKLEN or simvastatin alone. Inclusion in this study required 1) a baseline LDL-C level between 4.1 and 10.4 mmol/L (160 and 400 mg/dL) and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 5.8 mmol/L (range: 4.2-9.1 mmol/L) in the ezetimibe co-administered with simvastatin group compared to 5.7 mmol/L (range: 3.9-8.7 mmol/L) in the simvastatin monotherapy group. The patients received ZEKLEN (10/10, 10/20 or 10/40) or simvastatin alone (10 mg, 20 mg or 40 mg) for 6 weeks, ZEKLEN 10/40 or simvastatin 40 mg alone for the next 27 weeks, and open-label ZEKLEN (10/10, 10/20 or 10/40) for 20 weeks thereafter.

The primary hypothesis was that the percent change in LDL-C from baseline to Week 6 in the pooled ZEKLEN groups would be greater than in the pooled simvastatin monotherapy groups. At Week 6, ZEKLEN (all doses) lowered LDL-C significantly more than simvastatin (all doses) alone (49% vs 34% respectively). The results of the study at Week 6 are summarised in Table 6 and 6a. Results at Week 33 were consistent with those at Week 6. At Week 53, the end of the open-label extension, the effects on lipid parameters were maintained.

**Table 6**
**Absolute* Difference at Week 6 Between Pooled ZEKLEN Group and Pooled Simvastatin Group in Adolescent Patients with Heterozygous Familial Hypercholesterolaemia**

| | Total-C | LDL-C | Apo B | Non-HDL-C | TG† | HDL-C |
|---|---|---|---|---|---|---|
| **Mean absolute difference between treatment groups** | **-0.96** | **-0.93** | **-0.23** | **-0.95** | **-0.04** | **-0.01** |
| **95% Confidence Interval** | **-1.19, -0.73** | **-1.15, -0.72** | **-0.30, -0.17** | **-1.18, -0.72** | **-12, +0.04** | **-0.04, +0.03** |

* Mean (or median) absolute change from baseline (units are mmol/L for all parameters except Apo B, which is in g/L).
†For triglycerides, median absolute change from baseline.

**Table 6a**
**Mean Percent Difference at Week 6 Between Pooled ZEKLEN Group and Pooled Simvastatin Group in Adolescent Patients with Heterozygous Familial Hypercholesterolaemia**

| | Total-C | LDL-C | Apo B | Non-HDL-C | TG* | HDL-C |
|---|---|---|---|---|---|---|
| **Mean percent difference between treatment groups** | **-12%** | **-15%** | **-12%** | **-14%** | **-2%** | **+0.1%** |
| **95% Confidence Interval** | **-15%, -9%** | **-18%, -12%** | **-15%, -9%** | **-17%, -11%** | **-9, +4** | **-3, +3** |

*For triglycerides, median % change from baseline

From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ezetimibe co-administered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group.

The clinical safety and efficacy of ZEKLEN in children and adolescents (10-17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

The safety and efficacy of ezetimibe 10 mg co-administered with doses of simvastatin above 40 mg daily have not been studied in children and adolescents (10-17 years old) and are not recommended. The long-term efficacy of therapy with ZEKLEN in children and adolescents (10-17 years old) to reduce morbidity and mortality in adulthood has not been studied.

***Ezetimibe***
In two multicentre, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, race, and baseline LDL-C. In addition, ezetimibe had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.

***Simvastatin***
ZEKLEN contains simvastatin. In two large placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce the risk of total mortality by reducing CHD deaths, the risk of non-fatal myocardial infarction and stroke, and the need for coronary and non-coronary revascularisation procedures.

No incremental benefit of ZEKLEN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

***Homozygous Familial Hypercholesterolemia (HoFH)***
A double-blind, randomised, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analysed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Co-administered ezetimibe and simvastatin equivalent to ZEKLEN (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients co-administered ezetimibe and simvastatin equivalent to ZEKLEN (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

***Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)***
The Study of Heart and Renal Protection (SHARP) was a multinational, randomised, placebo-controlled, double-blind study conducted in 9,438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. Patients with a definite history of myocardial infarction (MI) or coronary revascularisation procedure, existing or planned renal transplant, recent acute uraemic emergency, evidence of active inflammatory muscle disease or creatine kinase (CK) >3xULN were excluded. For the first year, patients were randomised in a ratio of 4:4:1, respectively, to ZEKLEN 10/20, placebo, or simvastatin 20 mg daily. The 1-year simvastatin arm was included to enable the comparison of ZEKLEN to simvastatin alone with regard to safety and lipids. At 1 year the simvastatin-only arm was re-randomised 1:1 to ZEKLEN 10/20 or placebo. A total of 4,650 patients were allocated to ZEKLEN 10/20 and 4,620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 (ranging in age from 39 to 94.5 years old); 63% were male, 72% were Caucasian, and 23% were diabetic; and, for those not on dialysis, the median serum creatinine was 0.22 mmol/L and the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 $m^2$, with 94% of patients having an eGFR < 45 mL/min/1.73 $m^2$. There were no lipid entry criteria. Mean LDL-C at baseline was 2.8 mmol/L. As of the 1-year measurement, LDL-C was reduced 26% relative to placebo by simvastatin 20 mg alone and 38% for ZEKLEN 10/20. At the midpoint of the study (2.5 years) mean LDL-C reduction for ZEKLEN relative to placebo was 32%. All lipid measurements included patients no longer taking study medication.

The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the ZEKLEN (n=4,193) or placebo (n=4,191) groups. Secondary analyses included the same composite analysed for the full cohort

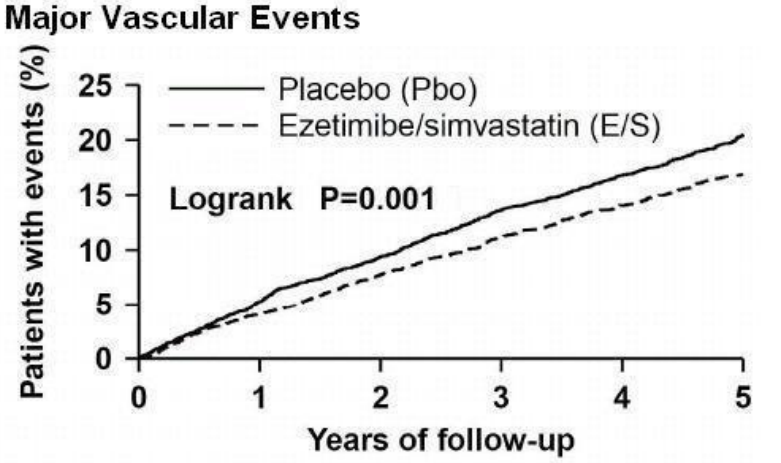
randomised (at study baseline or at year 1) to ZEKLEN (n=4,650) or placebo (n=4,620), as well as the components of this composite.

The primary endpoint analysis showed that ZEKLEN significantly reduced the risk of MVE (749 patients with events in the placebo group vs. 639 in the ZEKLEN group) with an absolute risk reduction of 2.3% (number needed to treat, 43) and a relative risk reduction of 16% (p=0.001) (see Figure 1). An analysis of major atherosclerotic events (MAE, a subset of the MVE composite that excluded non-coronary cardiac deaths and haemorrhagic stroke) showed that ZEKLEN significantly reduced the risk of MAE (526 (11.3%) of 4650 patients ever allocated to ZEKLEN and 619 (13.4%) of 4620 patients ever allocated to placebo), corresponding to an absolute risk reduction of 2.1% (number needed to treat, 48) and a relative risk reduction of 17% (p=0.002).

The risk reduction for the MVE composite was directionally consistent (i.e. ZEKLEN numerically superior to placebo) with that of the entire cohort of patients for the following key baseline predefined subgroups: age, gender, dialysis vs. non-dialysis, eGFR, diabetes, pre-existing atherosclerotic disease, blood pressure, or tertiles of baseline LDL-C.

Compliance rates with placebo and study medication declined over the course of the study. For example, at 20-25 months of follow-up, 68% of patients allocated to ezetimibe/simvastatin and 67% of patients allocated to placebo were taking 80% or more of the study medication, while at 44-49 months, compliance had fallen to 60% and 56%, respectively.

**Figure 1: Effect of ZEKLEN on the Primary Endpoint of Risk of Major Vascular Events**.




| At risk | | | | | | |
|---|---|---|---|---|---|---|
| Pbo | 4191 | 3807 | 3495 | 3177 | 2419 | 1239 |
| E/S | 4193 | 3868 | 3567 | 3273 | 2501 | 1232 |

The individual components of MVE in all randomised patients are presented in Table 7. ZEKLEN significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring ZEKLEN for nonfatal MI and cardiac death.

**Table 7**
**Major Vascular Events by Treatment Group in All Randomised Patients in SHARP[a]**

| Outcome | ZEKLEN 10/20 (N=4,650) | Placebo (N=4,620) | Risk Ratio (95% CI) | P-value |
|---|---|---|---|---|
| Major Vascular Events | 701 (15.1%) | 814 (17.6%) | 0.85 (0.77-0.94) | 0.001 |
| Nonfatal MI | 134 (2.9%) | 159 (3.4%) | 0.84 (0.66-1.05) | 0.12 |
| Cardiac Death | 253 (5.4%) | 272 (5.9%) | 0.93 (0.78-1.10) | 0.38 |
| Any Stroke | 171 (3.7%) | 210 (4.5%) | 0.81 (0.66-0.99) | 0.038 |
| Non-haemorrhagic Stroke | 131 (2.8%) | 174 (3.8%) | 0.75 (0.60-0.94) | 0.011 |
| Haemorrhagic Stroke | 45 (1.0%) | 37 (0.8%) | 1.21 (0.78-1.86) | 0.40 |
| Any Revascularisation | 284 (6.1%) | 352 (7.6%) | 0.79 (0.68-0.93) | 0.004 |
| Major Atherosclerotic Events (MAE)[b] | 526 (11.3%) | 619 (13.4%) | 0.83 (0.74-0.94) | 0.002 |

[a] Intention-to-treat analysis on all SHARP patients randomised to ZEKLEN or placebo either at baseline or year 1.
[b] MAE; defined as the composite of nonfatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any revascularisation.

No significant treatment effect of ZEKLEN on MVE was found in the subgroup of patients on dialysis at baseline compared with those not on dialysis at baseline. Among 3023 patients on dialysis at baseline, ZEKLEN reduced the risk of MVE by 6% (RR 0.94: 95% CI 0.80-1.09) compared with 22% (RR 0.78: 95% CI 0.69-0.89) among 6247 patients not on dialysis at baseline (interaction P=0.08).

Among patients not on dialysis at baseline, ZEKLEN did not reduce the risk of progressing to end-stage renal disease compared with placebo.

There were no significant differences between the ZEKLEN and placebo groups on all cause mortality, or on any specific cause of death.

The study design precluded drawing conclusions regarding the independent contribution of either ezetimibe or simvastatin to the observed effect, and was not able to provide evidence of efficacy for the combination of ZEKLEN 10/20 compared to either the lower dose combination (i.e. ZEKLEN 10/10) or to treatment with statin alone (i.e. simvastatin 20 mg).

## INDICATIONS

***Adults (≥18 years)***

***Primary Hypercholesterolaemia***
ZEKLEN is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:

- Patients not appropriately controlled with a statin or ezetimibe alone.
- Patients already treated with a statin and ezetimibe.

***Homozygous Familial Hypercholesterolaemia (HoFH)***
ZEKLEN is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

***Children and Adolescents 10-17 years***
***(pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche)***

***Heterozygous Familial Hypercholesterolaemia (HeFH)***
ZEKLEN is indicated as adjunctive therapy to diet in adolescent patients (10-17 years old) with heterozygous familial hypercholesterolaemia where use of a combination product is appropriate:

- Patients not appropriately controlled with a statin or ezetimibe alone.
- Patients already treated with a statin and ezetimibe.

***Homozygous Familial Hypercholesterolaemia (HoFH)***
ZEKLEN is indicated in adolescent patients (10-17 years old) with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).'

## CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see **PRECAUTIONS, *Use in Pregnancy and Use in Lactation***).
- Myopathy secondary to other lipid lowering agents.
- Concomitant administration of potent CYP3A4 inhibitors (eg. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and drugs containing cobicistat (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**).
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**)
- Concomitant use with fusidic acid (see **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

## PRECAUTIONS

No incremental benefit of ZEKLEN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. A beneficial effect of ezetimibe on cardiovascular morbidity and mortality has not been demonstrated.

***Myopathy/Rhabdomyolysis***
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with CK above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by 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 **INTERACTIONS WITH OTHER MEDICINES**). Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

**The risk of myopathy/rhabdomyolysis is dose related for simvastatin.** In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a major, large, long-term clinical trial (SEARCH) 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. This includes rhabdomyolysis for which the incidence was 0.1 to 0.2%, all allocated to simvastatin 80 mg/day. There is no universally accepted definition of rhabdomyolysis. In SEARCH, rhabdomyolysis was defined as a subset of myopathy with CK > 40 x ULN plus evidence of end organ damage (e.g. elevated creatinine, dark urine). Approximately half of all the myopathy cases occur during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-base therapies with similar LDL-C lowering efficacy. Therefore the 10/80 mg dose of ZEKLEN should only be used in patients at high risk for cardiovascular complications who have not achieve their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking ZEKLEN 10/80 mg for whom an interacting agent is needed, a lower dose of ZEKLEN or an alternative statin-ezetimibe regimen with less potential for drug-drug interactions should be used (see **CONTRAINDICATIONS; DOSAGE AND ADMINISTRATION**).

**All patients starting therapy with ZEKLEN, or whose dose of ZEKLEN is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. ZEKLEN therapy should be discontinued immediately if myopathy is diagnosed or suspected.** The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when

patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved (see **ADVERSE EFFECTS**). Periodic CK determinations may be considered in patients starting therapy with ZEKLEN or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 10/80 mg dose. There is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking ZEKLEN merit closer monitoring. Therapy with ZEKLEN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

In a clinical trial in which over 9,000 patients with chronic kidney disease were randomised to receive ZEKLEN 10/20 mg daily (n=4,650) or placebo (n=4,620) (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for ZEKLEN and 0.1% for placebo (See **ADVERSE EFFECTS**).

An increased risk of myopathy in Chinese subjects has been identified. In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n= 4 of 7367) compared with 0.24% for Chinese patients (n= 13 of 5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing ZEKLEN to any Asian patients and the lowest dose necessary should be employed.

***Drug interactions***

**Because ZEKLEN contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of ZEKLEN with the following medicines:**

Contraindicated medicines

- **Potent inhibitors of CYP3A4:** Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, or drugs containing cobicistat) is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with ZEKLEN should be suspended during the course of treatment (see **CONTRAINDICATIONS; INTERACTIONS WITH OTHER MEDICINES**).

- **Gemfibrozil, ciclosporin or danazol:** Concomitant use of these drugs with ZEKLEN is contraindicated (see **CONTRAINDICATIONS**).

- **Fusidic Acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see **INTERACTIONS WITH OTHER MEDICINES**). Fusidic acid must not be co-administered with statins (see **CONTRAINDICATIONS**). In patients where the use of systemic fusidic acid is considered essential, ZEKLEN should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any

symptoms of muscle weakness, pain or tenderness. ZEKLEN therapy may be reintroduced seven days after the last dose of fusidic acid.

Other medicines

- **Amiodarone:** In a large clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80mg and amiodarone. A significant interaction at lower simvastatin doses cannot be excluded. Therefore the dose of ZEKLEN should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone (see **DOSAGE AND ADMINISTRATION**; **INTERACTIONS WITH OTHER MEDICINES)**.

- **Calcium channel blockers:**
  - **Verapamil or diltiazem:** Co-administration of verapamil increased the incidence of myopathy to 0.7% (with simvastatin 40 mg) or 1% (with simvastatin 80 mg). Co-administration of diltiazem and simvastatin 80 mg led to a mean 70% increase in systemic exposure to simvastatin-derived HMG-CoA reductase inhibitory activity, with individual increases ranging up to 200%. In patients taking diltiazem with simvastatin 80 mg, the incidence of myopathy was about 1%. The dose of ZEKLEN should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see **DOSAGE AND ADMINISTRATION; INTERACTIONS WITH OTHER MEDICINES)**.

  - **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of ZEKLEN should not exceed 10/40 mg daily in patients receiving concomitant medication with amlodipine (see **DOSAGE AND ADMINISTRATION; INTERACTIONS WITH OTHER MEDICINES)**.

- **Lomitapide:** The dose of ZEKLEN should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide **(see INTERACTIONS WITH OTHER MEDICINES).**

- **Moderate inhibitors of CYP3A4**: Patients taking other medicines labelled as having a moderate inhibitor effect on CYP3A4 concomitantly with ZEKLEN, particularly higher ZEKLEN doses, may have an increased risk of myopathy. When co-administering ZEKLEN with a moderate inhibitor of CYP3A4, a dose adjustment of ZEKLEN may be necessary.

- **Inhibitors of Breast Cancer Resistance Protein (BCRP):** Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of ZEKLEN may be necessary. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of ZEKLEN should not exceed 10/20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see INTERACTIONS WITH OTHER MEDICINES).**

- **Other Fibrates:** The safety and effectiveness of ZEKLEN administered with fibrates have not been studied. **Therefore, the concomitant use of ZEKLEN and fibrates should be avoided. Concomitant use of gemfibrozil is contraindicated (see CONTRAINDICATIONS; INTERACTIONS WITH OTHER MEDICINES).**

- **Niacin (≥1 g/day):** ***The dose of ZEKLEN should not exceed 10/20 mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1 g/day.*** Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended release niacon/laropiprant 2g/40 mg. In comparison, in European/Non-Chinese patients the incidence of myopathy was approximately 0.05% for patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 0.09% for patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release niacin/laropiprant 2 g/ 40 mg. **While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in European/Non-Chinese patients, coadministration of ZEKLEN with lipid-modifying doses (≥1 g/day) of niacin is not recommended in Asian patients (see INTERACTIONS WITH OTHER MEDICINES).**

- **Anticoagulants:** If ZEKLEN is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (See **INTERACTIONS WITH OTHER MEDICINES**).

Prescribing recommendations for interacting agents are summarised in Table 8 below (see also **INTERACTIONS WITH OTHER MEDICINES, CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

**TABLE 8**
**Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**

| Interacting Agents | Prescribing Recommendations |
|---|---|
| Potent CYP3A4 Inhibitors, e.g.<br>Itraconazole<br>Ketoconazole<br>Posaconazole<br>Voriconazole<br>Erythromycin<br>Clarithromycin<br>Telithromycin<br>HIV protease inhibitors<br>Boceprevir<br>Telaprevir<br>Nefazodone<br>Cobicistat<br>Ciclosporin<br>Danazol<br>Gemfibrozil<br>Fusidic Acid | Contraindicated with ZEKLEN |
| Other fibrates (except fenofibrate)<br>Grapefruit juice | Use with ZEKLEN should be avoided |
| Niacin (≥1 g/day) | For Asian patients, not recommended with ZEKLEN |
| Amiodarone<br>Verapamil<br>Diltiazem<br>Niacin (≥1 g/day)<br>Elbasvir<br>Grazoprevir | Do not exceed ZEKLEN 10/20 mg daily |
| Amlodipine | Do not exceed ZEKLEN 10/40 mg daily |
| Lomitapide | For patients with HoFH, do not exceed ZEKLEN 10/40 mg daily |

**Liver Enzymes**
In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.7% overall for patients treated with ZEKLEN and appeared to be dose-related with an incidence of 2.6% for patients treated with ZEKLEN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with ZEKLEN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

In a controlled clinical study in which over 9,000 patients with chronic kidney disease were randomised to receive ZEKLEN 10/20 mg daily (n=4,650) or placebo (n=4,620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3 X ULN) was 0.7% for ZEKLEN and 0.6% for placebo (see **ADVERSE EFFECTS**).

It is recommended that LFTs be performed before treatment with ZEKLEN begins and periodically thereafter when clinically indicated. Patients titrated to the 10/80mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see **PRECAUTIONS*, Myopathy/ Rhabdomyolysis**).

There have been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with ZEKLEN, promptly interrupt therapy. If an alternate aetiology is not found do not restart ZEKLEN.

ZEKLEN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of ZEKLEN.

**Hepatic Insufficiency**
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZEKLEN is not recommended in these patients (see *Characteristics in Special Populations*).

**Interstitial Lung Disease**
Cases of interstitial lung disease have been reported with some statins, including simvastatin especially with long term therapy (see **ADVERSE EFFECTS**). Presenting features can 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.

**Carcinogenicity**
***ZEKLEN***
Carcinogenicity studies with ezetimibe/simvastatin combinations have not been performed.

***Ezetimibe***
Two-year dietary studies with ezetimibe alone in mice and rats showed no evidence of carcinogenic potential. The highest ezetimibe dose (500 mg/kg/day) in mice corresponds to exposure levels approximately 4 and ≥ 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively, based on AUC. Exposures in rats at the highest dose (1500 mg/kg/day in males and 500 mg/kg/day in females) correspond to approximately 2 and 14 times the adult human exposure for ezetimibe and total ezetimibe, respectively.

***Simvastatin***
Carcinogenicity studies have been conducted in mice at oral doses ranging from 1 to 400 mg/kg/day and in rats at doses of 1 to 100 mg/kg/day. Hepatocellular adenomas and carcinomas were observed in both sexes of both species at doses greater than 25 mg/kg/day. Plasma drug levels in rats at this no-effect dose level, expressed as the AUC for enzyme inhibitory activity, were 3 to 11 times greater than those in humans at the maximum recommended dose, whereas serum levels at the no-effect level in mice were similar to those in humans. Additional findings in mice were increased incidences of pulmonary adenomas at doses greater than 25 mg/kg/day, and of Harderian gland adenomas at 400 mg/kg/day. In rats, the incidence of thyroid follicular adenoma was increased in females at doses greater than 5 mg/kg/day and in males at doses greater than 25 mg/kg/day. These thyroid tumours were associated with focal cystic follicular hyperplasia, and may be a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance by the liver.

**Genotoxicity**
***ZEKLEN***
Ezetimibe alone or in combination with simvastatin did not cause gene mutation in bacteria or chromosomal damage in human peripheral lymphocytes or bone marrow cells in mice.

**Effects on fertility**
***ZEKLEN***
There are no human data addressing the effects of ezetimibe/simvastatin combinations on fertility. In animal reproductive/fertility studies, no effect on pregnancy rates was observed in rats treated orally with ezetimibe/simvastatin at up to 1000/12.5 mg/kg. These doses correspond to exposure levels (based on AUC) approximately 1x (free ezetimibe), 20x (total ezetimibe), 0.8x (simvastatin), and 72x (hydroxysimvastatin) that expected in humans over the ezetimibe/simvastatin combination dose range (10/10 mg to 10/80 mg).

**Thyroid Function**
***Simvastatin***
The concentration of serum thyroxin has been measured at baseline and at the end of simvastatin treatment in 785 patients enrolled in multicentre studies. The results of this analysis indicate that simvastatin has little if any effect upon thyroxin activity.

In one study involving 183 patients treated with simvastatin, four patients had TSH levels within the normal range before commencing simvastatin, but had an elevated TSH after two years of simvastatin therapy.

**Transient Hypotension**
***Simvastatin***
Three cases of symptomatic hypotension in the first few days following the start of simvastatin therapy have been reported. Two of the patients were on antihypertensive medication. The hypotension resolved with continued therapy with simvastatin.

**Neurological Effects**
***Simvastatin***

The neurological adverse effects reported to date include cases of peripheral neuropathy and paraesthesia possibly due to simvastatin.

**Effects on Spermatogenesis and Testosterone**
***Simvastatin***
In several studies of over 800 men with hypercholesterolaemia treated with simvastatin 20 mg to 80 mg per day for 12 to 48 weeks, basal testosterone levels were mildly decreased during simvastatin therapy, but there were no consistent changes in LH and FSH. In 86 men treated with simvastatin 20 mg to 80 mg per day, there was no impairment of hCG-stimulated testosterone secretion.

Testicular degeneration has been seen in two dog safety studies with simvastatin. Special studies designed to further define the nature of these changes have not met with success since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels, or duration of treatment. Simvastatin has been administered for up to two years to dogs at a dose of 50 mg/kg/day without any testicular effects.

***Use in Pregnancy (Category D)***

*Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

***ZEKLEN***
ZEKLEN is contraindicated during pregnancy. HMG-CoA reductase inhibitors, including simvastatin, a component of ZEKLEN, are contraindicated in pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor, or medicines containing an HMG-CoA reductase inhibitor, therapy during pregnancy.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia.

The safety of ezetimibe/simvastatin combinations in pregnant women has not been established.

Cholesterol and other products of the cholesterol biosynthesis pathway are essential components for foetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthetic pathway, ZEKLEN, which contains simvastatin, is contraindicated during pregnancy. ZEKLEN should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, ZEKLEN should be discontinued and the patient informed of the potential hazard to the foetus (see **CONTRAINDICATIONS**).

Ezetimibe in combination with statins in rats and rabbits resulted in higher exposures to ezetimibe and/or statins than either drug administered alone. Skeletal malformations (hemivertebrae in rats and shortened/filamentous tail associated with fused and reduced

number of caudal vertebrae in rabbits) and other less severe foetal abnormalities were observed in rats and rabbits dosed with ezetimibe/statin combinations during organogenesis.

***Simvastatin***
In two series of 178 and 134 cases where pregnant women took an HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman is exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to a HMG-CoA reductase inhibitor is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.
Maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, ZEKLEN should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with ZEKLEN should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see **CONTRAINDICATIONS**).

***Ezetimibe***
No clinical data on exposed pregnancies are available for ezetimibe.

Ezetimibe crossed the placenta in rats and rabbits. There was no evidence of foetal abnormalities in rats dosed with up to 1000 mg/kg/day ezetimibe by oral gavage during organogenesis, corresponding to exposures about 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively, based on AUC. There was an increase in the incidence of extra thoracic ribs in rabbits at doses of 250 to 1000 mg/kg/day, corresponding to exposures 0.5 to 1 times and 100 to 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively. The relevance of this finding to humans is not known.

***Use in Lactation***
There are no human or animal data addressing the use of ezetimibe/simvastatin combinations during lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, women taking ZEKLEN should not breastfeed their infants (see **CONTRAINDICATIONS**).

***Ezetimibe***
Studies in rats showed that ezetimibe is excreted in milk. Ezetimibe had no effects on pup development in rats treated with up to 1000 mg/kg/day ezetimibe during late pregnancy and lactation. Drug exposures (based on AUC) in pups were approximately 1.5% (free ezetimibe) and 50% (total ezetimibe) of maternal exposures. It is not known whether ezetimibe is excreted into human breast milk.

***Simvastatin***
Animal studies have shown that weight gain during lactation is reduced in the offspring of rats dosed with simvastatin at dosages of 12.5 to 25 mg/kg/day. There is no information from animal studies on whether simvastatin or its metabolites are excreted in breast milk.

**Use in the Elderly**

No dosage adjustment is required for elderly patients (see *Characteristics in Special Populations*). Because advanced age (≥65 years) is a predisposing factor for myopathy, ZEKLEN should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥65 years of age had an increased risk of myopathy compared to patients <65 years of age.

**Paediatric Use**

The use of ZEKLEN in children and adolescent patients (10-17 years old) is recommended only for patients with Heterozygous Familial Hypercholesterolaemia (HeFH) or Homozygous Familial Hypercholesterolaemia (HoFH).

However, clinical efficacy/safety study experience in paediatric and adolescent patients (aged 10 to 17 years) has been mostly limited to patients with Heterozygous Familial Hypercholesterolaemia (see **CLINICAL TRIALS**). There are also no long term (> 1 year) safety data in this population.

The clinical safety and efficacy of ZEKLEN in children and adolescents (10-17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

Safety and effectiveness of ZEKLEN in patients 10 to 17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. **Doses greater than 10/40 mg/day have not been studied in this population and are not recommended.** In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ZEKLEN for a treatment period > 33 weeks on growth, sexual maturation, intellectual and psychosocial development have not been studied (See **DOSAGE AND ADMINISTRATION; ADVERSE EFFECTS**; and **CLINICAL TRIALS,** ***Clinical Studies in Paediatric (10 to 17 Years of Age) Patients****).* Adolescent females should be counselled on appropriate contraceptive methods while on ZEKLEN therapy (see **CONTRAINDICATIONS; PRECAUTIONS**, ***Use in Pregnancy***).

The safety and efficacy of ZEKLEN doses above 10/40 mg daily have not been studied in children and adolescents (10-17 years old) and are not recommended. The long-term efficacy of therapy with ZEKLEN in children and adolescents (10-17 years old) to reduce morbidity and mortality in adulthood has not been studied.

ZEKLEN has not been studied in pre-menarchal girls or in pre-pubertal boys and is not recommended in children <10 years of age.

**Effects on ability to drive and use machines**

No studies of the effects on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with ZEKLEN may affect some people's ability to drive or operate machinery. Individual responses to ZEKLEN may vary (see **ADVERSE EFFECTS**).

## INTERACTIONS WITH OTHER MEDICINES

***ZEKLEN***
No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin. Specific pharmacokinetic drug interaction studies with ZEKLEN have not been performed.

ZEKLEN is bioequivalent to co-administered ezetimibe and simvastatin.

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.**

Contraindicated medicines
Concomitant use of the following medicines is contraindicated:

*Potent Inhibitors of CYP3A4*
In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolised by CYP3A4.

Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of ZEKLEN:

Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 (eg. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, or drugs containing cobicistat) is contraindicated (see **CONTRAINDICATIONS, PRECAUTIONS, *Myopathy/ Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**).

*Gemfibrozil, ciclosporin or danazol:* see **CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/ Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES***.*

*Gemfibrozil:* In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold; this increase is not considered clinically significant. No clinical data are available.

*Ciclosporin:* In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-

fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17).

In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 $m^2$) who was receiving multiple medications, including ciclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls.

In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100mg dose of ciclosporin on Day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of ciclosporin alone (see **CONTRAINDICATIONS and PRECAUTIONS**).

The pharmacokinetic interactions between ezetimibe at steady-state and ciclosporin also at steady-state have not been studied.

*Fusidic acid*
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of simvastatin with fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins. Where the use of fusidic acid is considered essential, ZEKLEN should be discontinued throughout the duration of fusidic acid treatment (see **CONTRAINDICATIONS** and **PRECAUTIONS, *Myopathy/Rhabdomyolysis***).

Other drug interactions

*Amiodarone*: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with ZEKLEN (see **DOSAGE AND ADMINISTRATION and PRECAUTIONS, *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**). During co-administration of amiodarone and simvastatin 80 mg in a large clinical trial, the risk of myopathy was approximately 6% (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**).

*Cholestyramine:* Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding ZEKLEN to cholestyramine may be lessened by this interaction.

*Calcium channel blockers:* The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see **DOSAGE AND ADMINISTRATION; PRECAUTIONS, *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**).

*Lomitapide:* The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see **DOSAGE AND ADMINISTRATION; PRECAUTIONS *Myopathy/Rhabdomyolysis***).

*Moderate inhibitors of CYP3A4:* Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy **(**see **PRECAUTIONS, *Myopathy/Rhabdomyolysis*).**

*Inhibitors of the Transport Protein OATP1B1*: Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see **CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis***).

*Inhibitors of Breast Cancer Resistance Protein (BCRP):* Simvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy. When co-administering simvastatin with an inhibitor of BCRP, a dose adjustment of ZEKLEN may be necessary (see **DOSAGE AND ADMINISTRATION; PRECAUTIONS, Myopathy/Rhabdomyolysis**).

*Fibrates:* Concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold; however, this increase is not considered clinically significant. The safety and effectiveness of ZEKLEN administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of ZEKLEN with fibrates is not recommended until use in patients is studied.

*Niacin:* In a study of 15 healthy adults, concomitant ZEKLEN (10/20mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%, 90% Confidence Interval (CI), -28 to 105) and nicotinuric acid (19%, 90% CI, -1 to 43) [n=13] administered as NIASPAN extended-release tablets (1000mg for 2 days and 2000mg for 5 days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9%, 90% CI, -2 to 22), total ezetimibe (26%, 90% CI, 10 to 44), simvastatin (20%, 90% CI, 3 to 40) and simvastatin acid (35%, 90% CI, -3 to 88) [n=15].

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day) of niacin (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis***).

*Colchicine:* There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of patients taking this combination is advised.

*Grapefruit juice*: Contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolised by CYP3A4. The effect of typical consumption (one 250-mL glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during ZEKLEN therapy (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis***).

*Coumarin derivatives:* In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting ZEKLEN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of ZEKLEN is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Concomitant administration of ezetimibe (10 mg once daily) for 11 days had no significant effect on bioavailability of a single dose 25 mg warfarin, administered on day 7, and prothrombin time in a cross-over study of twelve healthy adult males. There have been post-marketing reports of increased International Normalised Ratio in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications (see **PRECAUTIONS**).

The effect of ZEKLEN on the prothrombin time has not been studied.

*Antacids*: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

*Digoxin*: Concomitant administration of simvastatin and digoxin in normal volunteers resulted in a slight elevation (less than 0.3 ng/mL) in plasma drug concentrations (as measured by a digoxin radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

## ADVERSE EFFECTS

ZEKLEN (or co-administration of ezetimibe and simvastatin equivalent to ZEKLEN) has been evaluated for safety in approximately 12,000 patients in clinical trials. ZEKLEN was generally well tolerated.

The following common (≥1/100, <1/10) or uncommon (≥1/1000, <1/100) drug-related adverse experiences were reported in patients taking ZEKLEN (n=2404) and at a greater incidence than placebo (n=1340):

*Investigations:*
Common: ALT and/or AST increased; blood CK increased
Uncommon: blood bilirubin increased; blood uric acid increased; gamma-glutamyltransferase increased; international normalised ratio increased; protein urine present; weight decreased

*Nervous system disorders:*

Uncommon: dizziness; headache

*Gastrointestinal disorders:*
Uncommon: abdominal pain; abdominal discomfort; abdominal pain upper; dyspepsia; flatulence; nausea; vomiting

*Skin and subcutaneous tissue disorders:*
Uncommon: pruritus; rash

*Musculoskeletal and connective tissue disorders:*
Uncommon: arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; neck pain; pain in extremity

*General disorders and administration site conditions:*
Uncommon: asthenia; fatigue; malaise; oedema peripheral

*Psychiatric disorders:*
Uncommon: sleep disorder

The following common (≥1/100, <1/10) or uncommon (≥1/1000, <1/100); drug-related adverse experiences were reported in patients taking ZEKLEN (n=9595) and at a greater incidence than statins administered alone (n=8883):

*Investigations:*
Common: ALT and/or AST increased
Uncommon: blood bilirubin increased; blood CK increased; gamma-glutamyltransferase increased

*Nervous system disorders:*
Uncommon: headache; paresthaesia

*Gastrointestinal disorders:*
Uncommon: abdominal distension; diarrhoea; dry mouth; dyspepsia; flatulence; gastroesophageal reflux disease; vomiting

*Skin and subcutaneous tissue disorders:*
Uncommon: pruritus; rash; urticaria

*Musculoskeletal and connective tissue disorders:*
Common: myalgia
Uncommon: arthralgia; back pain; muscle spasms; muscular weakness; musculoskeletal pain; pain in extremity

*General disorders and administration site conditions:*
Uncommon: asthenia; chest pain; fatigue; oedema peripheral

*Psychiatric disorders:*
Uncommon: insomnia

***Paediatric (10 to 17 Years of Age) Patients***
In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n=248), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10X ULN). No cases of myopathy were reported (see **PRECAUTIONS *Paediatric Use*** and **CLINICAL TRIALS, *Clinical Studies in Paediatric (10 to 17 Years of Age) Patients***).

In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ZEKLEN for a treatment period > 33 weeks on growth, sexual maturation, intellectual and psychosocial development have not been studied (See **DOSAGE AND ADMINISTRATION; PRECAUTIONS**; and **CLINICAL TRIALS, *Clinical Studies in Paediatric (10 to 17 Years of Age) Patients***).

The study was not of sufficient duration to detect long term adverse events.

***Laboratory Values***
In controlled clinical co-administration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was 1.7% for patients treated with ZEKLEN. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see **PRECAUTIONS**).

Clinically important elevations of CK (≥ 10 X ULN) were seen in 0.2% of the patients treated with ZEKLEN.

***Patients with Chronic Kidney Disease***
In the Study of Heart and Renal Protection (SHARP) (see **CLINICAL TRIALS, Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)**), involving over 9,000 patients treated with ZEKLEN 10/20 daily (n=4,650) or placebo (n=4,620), the safety profiles were comparable during a median follow-up period of 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4% in patients treated with ZEKLEN, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with ZEKLEN and 0.1% in patients treated with placebo. Consecutive elevations of transaminases (>3 X ULN) occurred in 0.7% of patients treated with ZEKLEN compared with 0.6% of patients treated with placebo. In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for ZEKLEN, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

***Post-marketing Experience***
The adverse reactions reported for ZEKLEN are consistent with those previously reported with ezetimibe and/or simvastatin.

Additional adverse events reported commonly with **ezetimibe** during clinical trials:

*Gastrointestinal disorders:* gastritis
*Investigations:* liver function test abnormal
*Respiratory, thoracic and mediastinal disorders: cough*
*Metabolism and nutrition disorders:* decreased appetite
*Vascular disorders:* hot flush; hypertension
*General disorders and administration site conditions:* pain

Additional adverse events reported rarely, regardless of causality assessment, with **ezetimibe** during post-marketing use:

*Blood and lymphatic system disorders:* thrombocytopenia.
*Hepato-biliary disorders:* cholelithiasis, cholecystitis, hepatitis
*Musculoskeletal, connective tissue and bone disorders:* very rarely myopathy/rhabdomyolysis (see **PRECAUTIONS**)
*Psychiatric disorders:* depression
*Skin and subcutaneous tissue disorders:* Hypersensitivity reactions, including rash and urticaria (rare [≥ 1/10,000, < 1/1000]) and anaphylaxis and angioedema (very rare [< 1/10,000]), erythema multiforme
*Gastrointestinal disorders:* pancreatitis (very rare)
*Laboratory values*: increased CPK; elevations of liver transaminases

Additional adverse events reported rarely with **simvastatin** during clinical studies and/or post-marketing use:

*Blood and lymphatic system disorders:* anaemia;
*Gastrointestinal disorders:* constipation, pancreatitis;
*Hepatic disorders:* hepatitis/jaundice and very rarely, fatal and non-fatal hepatic failure;
*Reproductive system and breast disorders:* erectile dysfunction
*Musculoskeletal, connective tissue and bone disorders:* muscle cramps, myopathy, rhabdomyolysis (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis***).

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment: muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis***);

*Nervous system disorders:* peripheral neuropathy
*Respiratory, thoracic and mediastinal disorders:* interstitial lung disease
*Skin and subcutaneous tissue disorders:* alopecia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use.

These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

*Laboratory Values*: Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported with simvastatin.
Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.

## DOSAGE AND ADMINISTRATION

### Dosage Recommendations

The patient should be placed on a standard cholesterol-lowering diet before receiving ZEKLEN and should continue on this diet during treatment with ZEKLEN. ZEKLEN can be administered within the range of 10/10 mg/day to 10/80 mg/day. The usual starting dose is 10/10 mg/day to 10/40 mg/day. The dosage should be individualised according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. The 10/80mg dose of ZEKLEN should only be used in patients at 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 **PRECAUTIONS, *Myopathy/Rhabdomyolysis***). ZEKLEN should be taken as a single daily dose in the evening, with or without food. After initiation or titration of ZEKLEN, lipid levels may be analysed after 2 or more weeks and dosage adjusted, if needed.

***Dosage in Patients with Homozygous Familial Hypercholesterolaemia***
The recommended dosage for patients with homozygous familial hypercholesterolaemia is ZEKLEN 10/40 mg/day or 10/80 mg/day in the evening. The 10/80 mg dose should only be used when the benefits are expected to outweigh the potential risks (see **CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis***).

ZEKLEN should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

In patients taking lomitapide concomitantly with ZEKLEN, the dose of ZEKLEN should not exceed 10/40 mg/day (see **PRECAUTIONS**, ***Myopathy/Rhabdomyolysis*** and **INTERACTIONS WITH OTHER MEDICINES**).

***Patients with Renal Impairment/Chronic Kidney Disease***
In patients with mild renal insufficiency (estimated GFR ≥60 mL/min/1.73 $m^2$) no dosage adjustment is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 $m^2$, the dose of ZEKLEN is 10/20 mg once a day in the evening. In such patients, the use of higher doses should be closely monitored (See **PRECAUTIONS**, *Characteristics in Special Populations* and **CLINICALTRIALS**).

***Use in the Elderly***
No dosage adjustment is required for elderly patients (see *Characteristics in Special Populations*).

***Paediatric Use – Heterozygous or Homozygous Familial Hypercholesterolaemia***
Initiation of treatment must be performed under review of a specialist.

The use of ZEKLEN in children and adolescent patients (10-17 years old) is recommended only for patients with Heterozygous Familial Hypercholesterolaemia (HeFH) or Homozygous Familial Hypercholesterolaemia (HoFH).

There are no clinical safety and efficacy data on the use of ZEKLEN in children and adolescent patients (10-17 years old) with non-familial hypercholesterolaemia, or mixed hyperlipidaemia.

Adolescents 10 to 17 years old (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): The clinical experience in paediatric and adolescent patients (aged 10-17 years old) is limited and mostly includes children and adolescents (10-17 years old) with Heterozygous Familial Hypercholesterolaemia. There are also no long-term (>1 year) safety data in this population.

The recommended usual starting dose is 10/10 mg once a day in the evening. The recommended dosing range is 10/10 to **a maximum of 10/40 mg/day** (see *Characteristics in Patients [Special Populations]*).

Children < 10 Years: ZEKLEN is not recommended for use in children below age 10 due to very limited data on safety and efficacy (see *Characteristics in Patients [Special Populations]* and **PRECAUTIONS**). ZEKLEN has not been studied in pre-menarchal girls or in pre-pubertal boys and is not recommended in children <10 years.

***Hepatic Insufficiency***
No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with ZEKLEN is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction (see **PRECAUTIONS** and *Characteristics in Special Populations*).

***Co-administration with other medicines***
Dosing of ZEKLEN should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

In patients taking amiodarone, verapamil, diltiazem, ≥ 1 g/day of niacin, or products containing elbasvir or grazoprevir concomitantly with ZEKLEN, the dose of ZEKLEN should not exceed 10/20 mg/day (see **PRECAUTIONS, *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**).

In patients taking amlodipine concomitantly with ZEKLEN, the dose of ZEKLEN should not exceed 10/40 mg/day (see **CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis***, **INTERACTIONS WITH OTHER MEDICINES**).

The safety and effectiveness of ZEKLEN administered with fibrates have not been studied. Therefore, the concomitant use of ZEKLEN and fibrates should be avoided. **Concomitant use**

**of gemfibrozil is contraindicated** (see **CONTRAINDICATIONS**, **PRECAUTIONS *Myopathy/Rhabdomyolysis,* INTERACTIONS WITH OTHER MEDICINES**).

Because the incidence of myopathy when simvastatin is coadministered with lipid-modifying doses (greater than or equal to 1 g/day niacin) of niacin-containing products is higher in Chinese than in non-Chinese patients, coadministration of ZEKLEN with lipid-modifying doses of niacin-containing products is not recommended in Asian patients *(see* **PRECAUTIONS, *Myopathy/Rhabdomyolysis,* Drug Interactions*).***

## OVERDOSAGE

***ZEKLEN***
No specific treatment of overdosage with ZEKLEN can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral $LD_{50}$ for both species was ezetimibe ≥ 1000 mg/kg/simvastatin ≥ 1000 mg/kg.

For information on the management of overdose of ZEKLEN, contact the Poison Information Centre on 131126 (Australia).

***Ezetimibe***
In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, and 40mg/day to 13 patients with homozygous sitosterolemia for 26 weeks was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

***Simvastatin***
A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

## PRESENTATION AND STORAGE CONDITIONS

ZEKLEN is available in the following presentations:

ZEKLEN 10/10: [10mg Ezetimibe/ 10mg Simvastatin]: White to off-white, capsule shaped, biconvex compressed tablet marked with “311”. PA/Al/PVC/Al blister packs of 5, 10 and 30.
ZEKLEN 10/20 [10mg Ezetimibe/ 20mg Simvastatin]: White to off-white, capsule shaped, biconvex compressed tablet marked with “312”. PVC/PCTFE (Aclar)/ Aluminium blister packs of 5, 10 and 30.
ZEKLEN 10/40 [10mg Ezetimibe/ 40mg Simvastatin]: White to off-white, capsule shaped, biconvex compressed tablet marked with “313”. PVC/PCTFE (Aclar)/ Aluminium blister packs of 5, 10 and 30.

ZEKLEN 10/80 [10mg Ezetimibe/ 80mg Simvastatin]: White to off-white, capsule shaped, biconvex compressed tablet marked with “315”. PVC/PCTFE (Aclar)/ Aluminium blister packs of 5, 10 and 30.

Store below 25°C.

## NAME AND ADDRESS OF THE SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
LEVEL1, BUILDING A, 26 TALAVERA ROAD
MACQUARIE PARK NSW 2113
AUSTRALIA

## POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4).

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

25 November 2015

## DATE OF MOST RECENT AMENDMENT

This document was approved by the Therapeutic Goods Administration on 17 November 2017.