

NEW ZEALAND DATA SHEET

NAME OF MEDICINE

VISACOR
rosuvastatin 5 mg, 10 mg, 20 mg or 40 mg tablets

PRESENTATION

VISACOR 5 mg: A yellow, film-coated, round, biconvex, 7 mm tablet, impressed with "ZD4522 5". Each tablet contains 5 mg rosuvastatin as rosuvastatin calcium.

VISACOR 10 mg: A pink, film-coated, round, biconvex, 7 mm tablet, impressed with "ZD4522 10". Each tablet contains 10 mg rosuvastatin as rosuvastatin calcium.

VISACOR 20 mg: A pink, film-coated, round, biconvex, 9 mm tablet, impressed with "ZD4522 20". Each tablet contains 20 mg rosuvastatin as rosuvastatin calcium.

VISACOR 40 mg: A pink, film-coated, oval, biconvex, 11.4 x 6.9 mm tablet impressed with "ZD4522" on one side and "40" on the other side. Each tablet contains 40 mg rosuvastatin as rosuvastatin calcium.

USES

ACTIONS

Mechanism of action

Rosuvastatin is a selective, potent and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-

CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Clinical efficacy:

VISACOR reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (See Tables 1 and 2).

VISACOR also lowers the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratio's.

A therapeutic response to VISACOR is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Table 1 - Dose Response in Patients with Primary Hypercholesterolaemia (Type IIa and IIb) (Adjusted mean % change from baseline)

| Dose | N | LDL-C | Total-C | HDL-C | TG | NonHDL-C | ApoB | ApoA-I |
|---------|----|-------|---------|-------|-----|----------|------|--------|
| Placebo | 13 | -7 | -5 | 3 | -3 | -7 | -3 | 0 |
| 5 | 17 | -45 | -33 | 13 | -35 | -44 | -38 | 4 |
| 10 | 17 | -52 | -36 | 14 | -10 | -48 | -42 | 4 |
| 20 | 17 | -55 | -40 | 8 | -23 | -51 | -46 | 5 |
| 40 | 18 | -63 | -46 | 10 | -28 | -60 | -54 | 0 |

Table 2 - Dose Response in Patients with Hypertriglyceridaemia (Type IIb or Type IV) (Median % change from baseline)

| Dose | N | TG | LDL-C | Total-C | HDL-C | nonHDL-C | VLDL-C | VLDL-TG |
|---------|----|-----|-------|---------|-------|----------|--------|---------|
| Placebo | 26 | 1 | 5 | 1 | -3 | 2 | 2 | 6 |
| 5 | 25 | -21 | -28 | -24 | 3 | -29 | -25 | -24 |
| 10 | 23 | -37 | -45 | -40 | 8 | -49 | -48 | -39 |
| 20 | 27 | -37 | -31 | -34 | 22 | -43 | -49 | -40 |
| 40 | 25 | -43 | -43 | -40 | 17 | -51 | -56 | -48 |

The data in Tables 1 and 2 are confirmed by the broader clinical programme of over 5,300 patients given VISACOR.

In a study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given VISACOR from 20 mg to 80 mg in a force-titration design. All doses of VISACOR showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to 40 mg (12 weeks of treatment) LDL-C was reduced by 53%.

In a force-titration open label study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to VISACOR 20 - 40 mg titrated at a 6 week interval. In the overall population, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction by week 12 (considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose and 30% at the 40 mg dose. Of the 13 patients with an LDL-C of less than 15%, 3 had no response or an increase in LDL-C.

VISACOR is effective in a wide variety of patient populations with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race,

sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

The first 12-weeks' efficacy data from 5 Phase III efficacy trials (Trials 24 to 28) were pooled to investigate the overall effect of rosuvastatin 10 mg, and to look at comparisons with atorvastatin 10 mg (Trials 24 to 26), pravastatin 20 mg and simvastatin 20 mg (Trials 27 and 28). Table 3 presents key findings from these pools of data.

Overall, treatment with rosuvastatin at these doses resulted in a substantially better improvement in the atherogenic lipid profile than did treatment with the comparator statins.

| Table 3 Efficacy of rosuvastatin 10 mg versus atorvastatin 10 mg, pravastatin 20 mg and simvastatin 20 mg in subjects with Types IIa and IIb dyslipidaemia | | | | | |
|---|--------------------|-----|----------------------------------|-----------------------|--------------------|
| Trial number/time | Treatment | N | Lsmean of % change from baseline | | |
| | | | LDL-C | TG | HDL-C |
| Rosuvastatin overall | | | | | |
| 24 to 28 pooled/12 weeks | Rosuvastatin 5 mg | 630 | -41.4 ^a | -15.8 ^a | 7.7 ^a |
| | Rosuvastatin 10 mg | 615 | -47.2 ^a | -19.6 ^a | 9.0 ^a |
| Rosuvastatin versus atorvastatin | | | | | |
| 24 to 26 pooled/12 weeks | Rosuvastatin 5 mg | 390 | -41.9 ^{***} | -16.4 | 8.2 ^{**} |
| | Rosuvastatin 10 mg | 389 | -46.7 ^{***} | -19.2 | 8.9 ^{***} |
| | Atorvastatin 10 mg | 393 | -36.4 | -17.6 | 5.5 |
| Rosuvastatin versus pravastatin and simvastatin | | | | | |
| 27 and 28 pooled/12 weeks | Rosuvastatin 5 mg | 240 | -40.6 ^{+++###} | -14.9 | 6.9 |
| | Rosuvastatin 10 mg | 226 | -48.1 ^{+++###} | -20.2 ^{++##} | 9.1 ^{+.#} |
| | Pravastatin 20 mg | 252 | -27.1 | -12.4 | 6.2 |
| | Simvastatin 20 mg | 249 | -35.7 | -12.2 | 6.2 |

^a Mean of % change from baseline; Lsmean = Least squares mean; N = Number of subjects.

^{**} p<0.01 versus atorva; ^{***} = p<0.001 versus atorva; + = p<0.05 versus prava; ++ = p<0.01 versus prava; +++ = p<0.001 versus prava; # = p<0.05 versus simva; ## = p<0.01 versus simva; ### = p<0.001 versus simva.

The percentage of subjects who achieved joint European recommendations for LDL-C following 12 weeks of treatment with rosuvastatin (for the trial data pools) is shown in Table 4.

| Table 4 % of subjects reaching EAS targets for LDL-C levels at Week 12 | | | | | |
|---|--------------------|---------------|-------|------|-------------------|
| Trial number/time | Treatment | Risk category | | | |
| | | | Other | High | All |
| Rosuvastatin versus atorvastatin | | | | | |
| 24 to 26 pooled/12 weeks | Rosuvastatin 5 mg | | 77 | 37 | 49 |
| | Rosuvastatin 10 mg | | 88 | 59 | 66 ^{***} |
| | Atorvastatin 10 mg | | 69 | 23 | 36 |
| Rosuvastatin versus pravastatin and simvastatin | | | | | |
| 27 and 28 pooled/12 weeks | Rosuvastatin 5 mg | | 63 | 44 | 52 ⁺⁺⁺ |
| | Rosuvastatin 10 mg | | 84 | 64 | 74 ⁺⁺⁺ |
| | Pravastatin 20 mg | | 16 | 8 | 12 |
| | Simvastatin 20 mg | | 56 | 22 | 37 |

*** p<0.001 versus atorvastatin; +++ p<0.001 versus pravastatin and simvastatin

Active-Controlled Study: VISACOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study of 2,239 patients with Type IIa and IIb hypercholesterolaemia. After randomization, patients were treated for 6 weeks with a single daily dose of either VISACOR, atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 5). The primary endpoint for this study was the percent change from baseline in LDL-C at week 6.

Figure 1. Percent LDL-C Change by Dose of VISACOR, Atorvastatin, Simvastatin and Pravastatin at Week 6 in Patients With Type IIa/IIb Dyslipidaemia

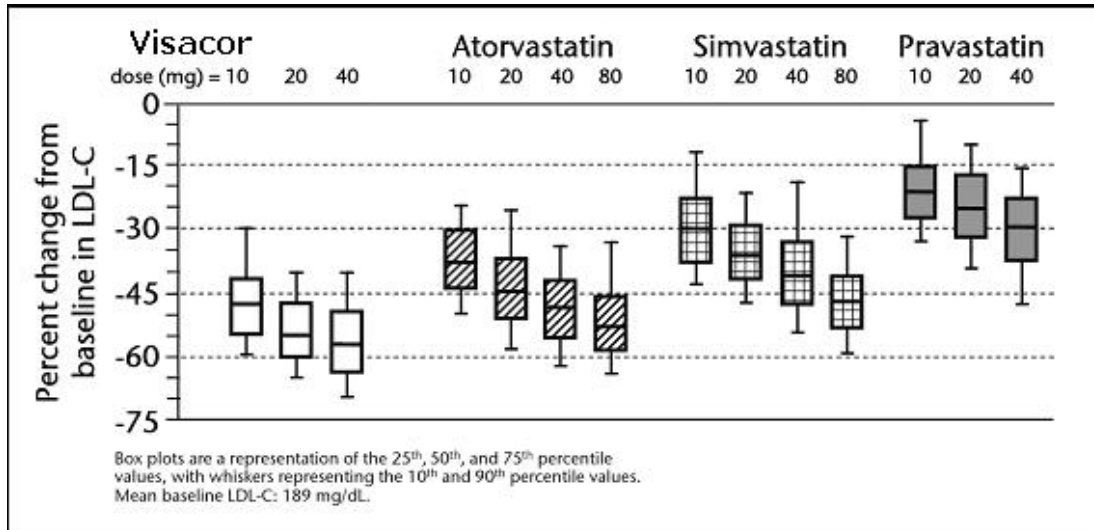


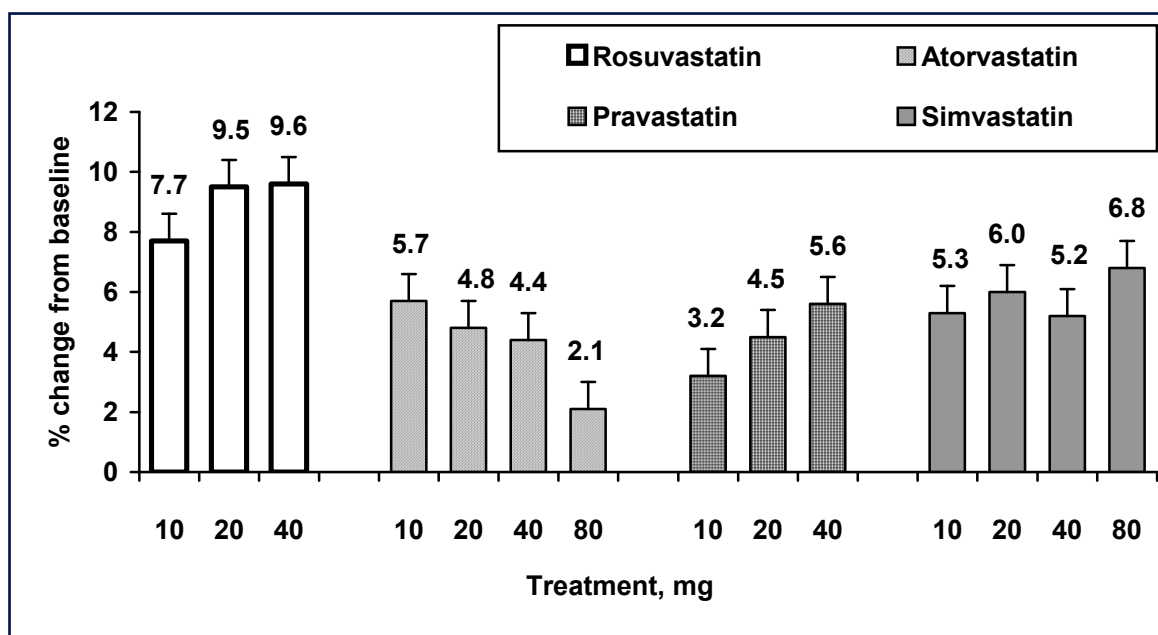
Table 5. LSMean[§] % change in LDL-C from baseline to Week 6 for each statin treatment group. N = number of patients at each dose of each statin.

| Treatment | TREATMENT DAILY DOSE | | | | | | | |
|--------------|----------------------|-------------------|-------|--------------------------------|-------|--------------------------------|-------|-------------------|
| | 10 mg | | 20 mg | | 40 mg | | 80 mg | |
| | N | Mean (95%CI) | N | Mean (95%CI) | N | Mean (95%CI) | N | Mean (95%CI) |
| Rosuvastatin | 156 | -46 (-48, -44) | 160 | -52 [†] (-54, -50) | 157 | -55 [‡] (-57, -53) | - | - |
| Atorvastatin | 158 | -37 (-39, -35) | 154 | -43 (-45, -41) | 156 | -48 (-50, -46) | 165 | -51 (-53, -49) |
| Pravastatin | 160 | -20 (-22, -18) | 164 | -24 (-26, -22) | 161 | -30 (-32, -28) | - | - |
| Simvastatin | 165 | -28 (-30, -26) | 162 | -35 (-37, -33) | 158 | -39 (-41, -37) | 163 | -46 (-48, -44) |

- * Rosuvastatin 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. (p<0.002)
- † Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)
- ‡ Rosuvastatin 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg (p<0.002)
- § Corresponding standard errors are approximately 1.00

The percent change from baseline in HDL-C at week 6 is shown in Figure 2 below:

Figure 2. Mean (LS mean) Percent Change from Baseline in HDL-C to Week 6



$p < 0.002$ Rosuvastatin 10 mg vs Pravastatin 10 mg

$p < 0.002$ Rosuvastatin 20 mg vs Atorvastatin 20 mg, 40 mg, 80 mg; Pravastatin 20 mg, 40 mg; Simvastatin 40 mg

$p < 0.002$ Rosuvastatin 40 mg vs Atorvastatin 40 mg, 80 mg; Pravastatin 40 mg; Simvastatin 40 mg

Data presented as LS means \pm SE

The mean percent change in HDL-C from baseline to Week 6 for each statin treatment group represented in Figure 2 is summarised with 95% CI in Table 6.

Table 6. LS Mean % change in HDL-C from baseline to Week 6 for each statin treatment group. N = number of patients at each dose of each statin.

| Treatment | TREATMENT DAILY DOSE | | | | | | | |
|--------------|----------------------|--------------|-------|--------------|-------|---------------|-------|--------------|
| | 10 mg | | 20 mg | | 40 mg | | 80 mg | |
| | N | Mean (95%CI) | N | Mean (95%CI) | N | Mean (95%CI) | N | Mean (95%CI) |
| Rosuvastatin | 156 | 8 (6, 9) | 160 | 9 (8, 11) | 157 | 10 (8, 11) | - | - |
| Atorvastatin | 158 | 6 (4, 7) | 154 | 5 (3, 7) | 156 | 4 (3, 6) | 165 | 2 (0, 4) |
| Pravastatin | 160 | 3 (2, 5) | 164 | 4 (3, 6) | 161 | 6 (4, 7) | - | - |
| Simvastatin | 165 | 5 (4, 7) | 162 | 6 (4, 8) | 158 | 5 (4, 6) | 163 | 7 (5, 8) |

Hypertriglyceridaemia (Fredrickson Type IIb & IV)

In a double blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, VISACOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 7).

Table 7. Dose-Response in Patients With Primary Hypertriglyceridaemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

| Dose | Placebo N=26 | Rosuvastatin 5 mg N=25 | Rosuvastatin 10 mg N=23 | Rosuvastatin 20 mg N=27 | Rosuvastatin 40 mg N=25 |
|---------------|-----------------|------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Triglycerides | 1 (-40, 72) | -21 (-58, 38) | -37 (-65, 5) | -37 (-72, 11) | -43 (-80, -7) |
| NonHDL-C | 2 (-13, 19) | -29 (-43, -8) | -49 (-59, -20) | -43 (-74, -12) | -51 (-62, -6) |
| VLDL-C | 2 (-36, 53) | -25 (-62, 49) | -48 (-72, 14) | -49 (-83, 20) | -56 (-83, 10) |
| Total-C | 1 (-13, 17) | -24 (-40, -4) | -40 (-51, -14) | -34 (-61, -11) | -40 (-51, -4) |
| LDL-C | 5 (-30, 52) | -28 (-71, 2) | -45 (-59, 7) | -31 (-66, 34) | -43 (-61, -3) |
| HDL-C | -3 (-25, 18) | 3 (-38, 33) | 8 (-8, 24) | 22 (-5, 50) | 17 (-14, 63) |

High Risk Hypercholesterolaemic Patients

In a 26 week double-blind forced titration study, 871 high risk hypercholesterolaemic patients with established CHD or multiple risk factors for CHD, were randomised to receive either rosuvastatin or atorvastatin. Patients in the rosuvastatin arm were titrated to 40 mg, while in the atorvastatin arm patients were titrated to 80 mg. The primary objective of the study was to compare rosuvastatin 40 mg with atorvastatin 80 mg in high risk patients, by measuring the percentage change in LDL-C from baseline to Week 8. Table 8 summarises the results for the mean percentage change from baseline at 8 weeks in lipid and lipoprotein variables.

Table 8: Summary of the mean percentage changes in lipid and lipoprotein variables in high risk hypercholesterolaemic patients after 8 weeks treatment with either rosuvastatin 40 mg or atorvastatin 80 mg.

| Variable | Mean % change [‡] RSV 40 mg n=432 | Mean % change [‡] ATV 80 mg n=439 | Difference in ls mean% changes | 95% CI [§] | p value [¥] |
|-----------|---|---|--------------------------------------|---------------------|----------------------|
| LDL-C | -55.89 | -52.18 | -3.71 | -5.61 to -1.82 | <0.001 |
| HDL-C | 9.58 | 4.35 | 5.23 | 3.04 to 7.43 | <0.001 |
| TC | -40.40 | -39.27 | -1.13 | -2.63 to 0.36 | 0.138 ^b |
| non-HDL-C | -50.75 | -48.27 | -2.48 | -4.25 to -0.72 | 0.006 |
| Apo B | -44.64 | -42.29 | -2.35 | -4.17 to -0.52 | 0.012 |
| Apo-AI | 4.20 | -0.47 | 4.67 | 2.71 to 6.63 | <0.001 |
| TG | -22.21 | -27.02 | 4.81 | 1.10 to 8.53 | 0.011 ^a |

[‡] Mean % change from baseline

[§] 95% confidence interval for the difference between the least squares means

[¥] p < 0.05 was statistically significant

^a statistically significant in favour of atorvastatin

^b ns = not significant

RSV = rosuvastatin; ATV = atorvastatin; ls = least squares

Atherosclerosis

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or

placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; $p < 0.0001$]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year ($p < 0.0001$)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of VISACOR 40mg. The 40mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see DOSAGE AND ADMINISTRATION).

Children and Adolescents with Hypercholesterolaemia

In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n = 176, 97 male and 79 female) followed by a 40-week (n = 173, 96 male and 77 female), open label, rosuvastatin dose titration phase, patients 10 – 17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 – 13 years and approximately 17%, 18%, 40% and 25% were Tanner stage II, III, IV and V respectively.

Rosuvastatin reduced LDL-C (primary end point), total cholesterol and ApoB levels. Results are shown in Table 9 below.

Table 9 Lipid-modifying effects of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia (least-squares mean percent change from baseline to week 12)

| Dose (mg) | N | LDL-C | HDL-C | Total-C | TG | Non-HDL-C | ApoB | ApoA-1 |
|-----------|----|-------|-------|---------|-------|-----------|-------|--------|
| Placebo | 46 | -0.7 | 6.9 | -0.0 | 5.1 | -0.9 | -1.7 | 2.8 |
| 5 | 42 | -38.3 | 4.2 | -29.9 | 0.3 | -36.1 | -31.7 | 1.8 |
| 10 | 44 | -44.6 | 11.2 | -34.2 | -13.6 | -43.0 | -38.1 | 5.4 |
| 20 | 44 | -50.0 | 8.9 | -38.7 | -8.1 | -47.5 | -40.7 | 4.0 |

PHARMACOKINETICS

VISACOR is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Absorption increases linearly over the dose range. The half life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20%. There is minimal accumulation on repeated once daily dosing.

Rosuvastatin undergoes first pass extraction in the liver which is the primary site of cholesterol synthesis and LDL-C clearance.

Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. The parent compound accounts for greater than 90% of the circulating active HMG CoA reductase inhibitor activity.

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

Special populations:

Age and sex:

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race:

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Renal insufficiency:

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment ($CrCl < 30$ mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers.

Hepatic insufficiency:

In a study in subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in the 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores.

INDICATIONS

VISACOR should be used as an adjunct to diet when the response to diet and exercise is inadequate.

In patients with hypercholesterolemia

VISACOR is indicated to:

- Reduce elevated LDL-C, Total Cholesterol, triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non familial) and mixed dyslipidaemia (Fredrickson Types IIa and IIb). VISACOR also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG, the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I in these populations.

- Treat isolated hypertriglyceridaemia (Fredrickson Type IV hyperlipidaemia).
- Reduce Total Cholesterol and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to diet and other lipid lowering treatments (eg. LDL apheresis) or alone if such treatments are unavailable.

Prior to initiating therapy with rosuvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

DOSAGE AND ADMINISTRATION

The usual dose range is 10 - 40 mg orally once a day.

The dosage of VISACOR should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the start dose. However, if necessary, dose adjustment can be made at 2 to 4 week intervals. (See ACTIONS).

A dose of 40 mg once a day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once a day is assessed. It is recommended that the 40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 40 mg must not be exceeded in any patient taking rosuvastatin.

VISACOR may be given at any time of the day, with or without food.

PRIMARY HYPERCHOLESTEROLAEMIA (INCLUDING HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA), MIXED DYSLIPIDAEMIA AND ISOLATED HYPERTRIGLYCERIDAEMIA

The usual start dose is 10 mg once a day.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg may be considered.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA

For patients with homozygous familial hypercholesterolaemia a start dose of 20 mg once a day is recommended.

USE IN CHILDREN

Experience is limited to a small number of children (aged 8 years and above) with homozygous familial hypercholesterolaemia.

USE IN THE ELDERLY

The usual dose range applies.

DOSAGE IN PATIENTS WITH RENAL INSUFFICIENCY

The usual dose range applies in patients with mild to moderate renal impairment.

For patients with severe renal impairment the dose of VISACOR should not exceed 10 mg once daily. (See PHARMACOKINETICS and CONTRAINDICATIONS).

DOSAGE IN PATIENTS WITH HEPATIC INSUFFICIENCY

The usual dose range applies in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should start therapy with VISACOR 10 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above VISACOR 10 mg should be carefully considered. (See PHARMACOKINETICS).

RACE

A 5 mg starting dose of VISACOR should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see WARNINGS AND PRECAUTIONS and PHARMACOKINETICS). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolemia is not adequately controlled at doses up to 20 mg/daily.

CONCOMITANT THERAPY

VISACOR has been shown to have additive efficacy when used in combination with fenofibrate and niacin. VISACOR can also be used in combination with bile acid sequestrants. (See WARNINGS AND PRECAUTIONS).

INTERACTIONS REQUIRING DOSE ADJUSTMENTS**Cyclosporin:**

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant VISACOR and cyclosporin. For the VISACOR dose range (10-40 mg), this combination is not recommended.

Gemfibrozil:

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant VISACOR and gemfibrozil. Patients taking this combination should start therapy with VISACOR 10 mg once daily and should not exceed a dose of VISACOR 20 mg once daily. (See WARNINGS AND PRECAUTIONS and INTERACTIONS).

CONTRAINDICATIONS

VISACOR is contraindicated in patients with hypersensitivity to any component of this product.

VISACOR is contraindicated in patients with active liver disease or persistent, unexplained elevations in transaminases.

VISACOR is contraindicated during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

VISACOR 40 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in rosuvastatin plasma levels may occur
- severe renal impairment (CrCl < 30 mL/min)
- asian patients
- concomitant use of fibrates

WARNINGS AND PRECAUTIONS

LIVER:

Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

As with other HMG-CoA reductase inhibitors, VISACOR should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

SKELETAL MUSCLE:

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle eg. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reported rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. VISACOR therapy should be discontinued if CK levels are markedly elevated (>10xULN) or if myopathy is diagnosed or suspected.

In VISACOR trials there was no evidence of increased skeletal muscle effects when VISACOR was dosed with any concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with cyclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

VISACOR should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur (see PHARMACOKINETICS).

Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

VISACOR should be temporarily withheld in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe, metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

DIABETES MELLITUS

As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin. An increased frequency of diabetes has been reported with rosuvastatin in patients with risk factors for diabetes (see Adverse Effects and Pharmacodynamics)

RACE:

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see DOSAGE AND ADMINISTRATION and PHARMACOKINETICS).

INTERSTITIAL LUNG DISEASE

Exceptional cases of interstitial lung disease have been reported with some statins, 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 a patient has developed interstitial lung disease, statin therapy should be discontinued.

CHILDREN AND ADOLESCENTS 10 TO 17 YEARS OF AGE:

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking VISACOR is limited to a one year period (See Uses).

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Pharmacology testing revealed no evidence of a sedative effect of VISACOR. From the safety profile, VISACOR is not expected to adversely affect the ability to drive or use machines.

PREGNANCY AND LACTATION

The safety of VISACOR during pregnancy and whilst breast feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures (see CONTRAINDICATIONS).

ADVERSE EFFECTS

VISACOR is generally well tolerated. The adverse events seen with VISACOR are generally mild and transient. In controlled clinical trials, less than 4% of VISACOR treated patients were withdrawn due to adverse events. This withdrawal rate was comparable to that reported in patients receiving placebo.

| | |
|-------------------------------|---|
| Common (>1/100, <1/10) | Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain. |
|-------------------------------|---|

Uncommon (>1/1000, <1/100) Pruritus, rash and urticaria.

Rare (>1/10,000, <1/1000) Myopathy (including myositis), hypersensitivity reactions (including angioedema), rhabdomyolysis, pancreatitis.

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to increase with increasing dose.

SKELETAL MUSCLE EFFECTS:

Rare cases of rhabdomyolysis, which were occasionally associated with impairment of renal function have been reported with rosuvastatin and with other marketed statins.

LABORATORY EFFECTS:

As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases and CK has been observed in a small number of patients taking rosuvastatin. Increases in HbA1c have also been observed in patients treated with rosuvastatin (See PHARMACODYNAMICS). Abnormal urinalysis testing (Dipstick positive proteinuria) has been seen in a small number of patients taking VISACOR and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.

OTHER EFFECTS:

In a long term controlled clinical trial VISACOR was shown to have no harmful effects on the ocular lens.

In VISACOR treated patients, there was no impairment of adrenocortical function.

POST MARKETING EXPERIENCE

In addition to the above, the following adverse events have been reported during post marketing experience for VISACOR:

Hepatobiliary disorders: Very rare: jaundice, hepatitis; *Rare:* increased hepatic transaminases.

Musculoskeletal disorders: Very rare: arthralgia.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

Nervous system disorders: Very rare: memory loss.

Psychiatric disorders: Unknown: depression, sleep disorders (including insomnia and nightmares).

The following adverse events have been reported with some statins:

- Sexual dysfunction

- Exceptional cases of interstitial lung disease, especially with long term therapy.

CHILDREN AND ADOLESCENTS 10 TO 17 YEARS OF AGE

The safety profile of VISACOR is similar in children or adolescent patients and adults although CK elevations $>10 \times$ ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in clinical trials of children and adolescents. However, the same warnings and precautions for use in adults also apply to children and adolescents (See Warnings and Precautions).

INTERACTIONS

WARFARIN:

The pharmacokinetics of warfarin are not significantly affected following co-administration with VISACOR. However, as with other HMG-CoA reductase inhibitors, co-administration of VISACOR and warfarin may result in a rise in INR compared to warfarin alone. In patients taking vitamin K antagonists monitoring of INR is recommended both at initiation or cessation of therapy with VISACOR or following dose adjustment.

CYCLOSPORIN:

Co-administration of VISACOR with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state AUC(0-t) increased up to 7-fold over that seen in healthy volunteers administered the same dose. (See DOSAGE AND ADMINISTRATION).

GEMFIBROZIL:

Concomitant use of VISACOR and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC(0-t). (See DOSAGE AND ADMINISTRATION).

LOPINAVIR / RITONAVIR:

In a pharmacokinetic study, co-administration of VISACOR and a combination product of two protease inhibitors (400 mg lopinavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately 2-fold and 5-fold increase in rosuvastatin steady-state AUC₍₀₋₂₄₎ and C_{max} respectively. Any interaction between VISACOR and other protease inhibitors has not been examined.

Consideration should be given both to the benefit of lipid lowering by the use of VISACOR in HIV patients receiving lopinavir / ritonavir and the potential risks of this increased exposure to rosuvastatin when initiating and up-titrating VISACOR treatment.

ANTACIDS:

The simultaneous dosing of VISACOR with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after VISACOR. The clinical relevance of this interaction has not been studied.

CYTOCHROME P450 ENZYMES:

In vitro and in vivo data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer).

OTHER MEDICATIONS:

There were no clinically significant interactions with an oral contraceptive, digoxin or fenofibrate.

In clinical studies VISACOR was co-administered with antihypertensive agents, antidiabetic agents and hormone replacement therapy. These studies did not produce any evidence of clinically significant adverse interactions.

OVERDOSAGE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Haemodialysis is unlikely to be of benefit.

PHARMACEUTICAL PRECAUTIONS**STORAGE CONDITIONS**

Blister Packs: Store below 30°C

SHELF-LIFE

3 years

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Blister packs containing 7 (VISACOR 5 and 10 mg only) or 30 tablets.

FURTHER INFORMATION**PRE-CLINICAL SAFETY INFORMATION**

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

EXCIPIENTS**Tablet core:**

- Crospovidone
- Lactose monohydrate

- Microcrystalline cellulose
- Calcium phosphate
- Magnesium stearate

Tablet coat:

- Titanium dioxide (E171)
- Ferric oxide, red (E172) (10 mg, 20 mg, 40 mg only)
- Ferric oxide, yellow (E172) (5 mg only)
- Glycerol triacetate
- Lactose monohydrate
- Hypromellose

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