PERMITTED DAILY EXPOSURE FOR ROSUVASTATIN CALCIUM

1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Rosuvastatin Calcium have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

Rosuvastatin is a statin medication, used to prevent cardiovascular disease in those at high risk and treat abnormal lipids. It is recommended to be used together with dietary changes, exercise, and weight loss. It is taken by mouth.

Common side effects include abdominal pain, nausea, headaches, and muscle pains. Serious side effects may include rhabdomyolysis, liver problems and diabetes. Use during pregnancy may harm the baby. Like all statins, Rosuvastatin works by inhibiting HMG-CoA reductase, an enzyme found in the liver that plays a role in producing cholesterol.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol.

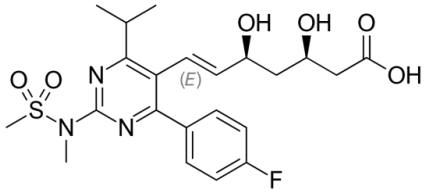
IUPAC name: (3R,5S,6E)-7-[4-(4-Fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid

Chemical Abstract Services (CAS) Registry Number: 287714-41-4

Molecular Weight: 481.539 g·mol−1

Chemical Formula: $C_{22}H_{28}FN_3O_6S$

Molecular Structure:



4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
TOXICITY	**YES**	**NO**	**UNKNOWN**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmental Toxicant	-	√	-
Highly Sensitizing potential	-	√	-

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SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDLC and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. Some studies have also shown that the total-C/HDL-C ratio is the best predictor of coronary artery disease. In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.
Pharmacokinetics data	**Absorption:** Rosuvastatin is administered orally following which Rosuvastatin, the active moiety, is rapidly absorbed, reaching peak plasma concentration 3 to 5 hours after dosing. Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increase in proportion to Rosuvastatin dose. The absolute bioavailability of Rosuvastatin is approximately 20% and there is no accumulation on repeated dosing. Rosuvastatin may be given with or without food. Administration in the morning or evening did not affect the rate and extent of absorption nor the ability of Rosuvastatin to reduce LDL-C. **Distribution:** Rosuvastatin undergoes first pass extraction in the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The mean volume of distribution at steady state of Rosuvastatin is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations. **Metabolism:** Rosuvastatin is not extensively metabolised with approximately 10% of a radiolabeled dose recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin, which is formed principally by cytochrome P450 2C9, and in in vitro studies has demonstrated to have approximately one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin. The parent compound accounts for greater than 87% of the circulating active HMG-CoA reductase inhibitor activity. **Excretion:** Following an oral dose, Rosuvastatin and its metabolites are primarily excreted in the faeces (90%) with the remainder being excreted in the urine. Fecal recovery represents absorbed drug, metabolites in the bile and unabsorbed drug. The elimination half-life (t½) of Rosuvastatin is approximately 19 hours and does not increase with increasing doses.

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Case 1: Rosuvastatin was shown to be of low acute toxicity following administration of single doses to rats and dogs by oral and intravenous routes. There were no mortalities in rats given an oral dose of 1000 mg/kg or 2000 mg/kg, and other than depression of bodyweight at 2000 mg/kg, there were no treatment-related effects at either dose level. Dogs received oral doses of 1000 mg/kg or 2000 mg/kg with vomiting on the day of dosing observed as the major clinical finding in both sexes. Biochemical changes (increased plasma enzymes, decreased lipids) and hematological change (increased white blood cells) were found in dogs given an oral dose of up to and including 2000 mg/kg. Lethality was observed immediately after dosing in 1/1 of rats given an intravenous dose of 500 mg/kg but two rats given 250 mg/kg intravenously showed slight hypopnea and weakness soon after dosing with no subsequent effects. The results are summarized below:

Species	Route	Dose Levels for One or Both Sexes (mg/kg)	Mortalities
Rat	Oral	1000 and 2000	0/1 at 1000 mg/kg; 0/2 at 2000 mg/kg
Rat	Intravenous	250 and 500	1/1 died at 500 mg/kg; 0/2 at 250 mg/kg
Rat	Oral	1000 and 2000	0/12 at 1000 mg/kg; 0/12 at 2000 mg/kg
Dog	Oral	1000 and 2000	0/2 at 1000 mg/kg; 0/2 at 2000 mg/kg

Case 2: Acute Exposure/Rosuvastatin was shown to be of low acute toxicity following administration of single doses to rats and dogs by oral and intravenous routes. There were no mortalities in rats given an oral dose of 1000 mg/kg or 2000 mg/kg, and other than depression of bodyweight at 2000 mg/kg, there were no treatment-related effects at either dose level. Dogs received oral doses of 1000 mg/kg or 2000 mg/kg with vomiting on the day of dosing observed as the major clinical finding in both sexes. Biochemical changes (increased plasma enzymes, decreased lipids) and hematological change (increased white blood cells) were found in dogs given an oral dose of up to and including 2000 mg/kg. Lethality was observed immediately after dosing in 1/1 of rats given an intravenous dose of 500 mg/kg but two rats given 250 mg/kg intravenously showed slight hypopnea and weakness soon after dosing with no subsequent effects.

Repeated Dose Toxicity (Chronic Toxicity)

Case 1: In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60 or 80 mg/kg/day, the incidence of uterine polyps was statistically significantly increased only in females at the dose of 80 mg/kg/day. This dose produced a plasma AUC (0-24) value approximately 8 times higher (after correction for interspecies differences in protein binding) than the human plasma drug exposure after a 40 mg dose at steady-state. Increased incidences of polyps observed at 2, 20 and 60 mg/kg/day were not

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SUMMARY OF HAZARD IDENTIFICATION:	
	statistically different from the control group not exposed to Rosuvastatin. The 60 mg/kg/day dose produced a plasma AUC (0 -24) value approximately 5 times higher (after correction for interspecies differences in protein binding) than the mean human exposure after a 40 mg dose at steady-state. The occurrence of uterine polyps in old female rats is well-known and is considered benign tumors and lesions termed non-neoplastic in humans. **Case 2:** In a 107-week carcinogenicity study in mice given 10, 60, 200 or 400 mg/kg/day, the 400 mg/kg/day dose was poorly tolerated, resulting in early termination of this dose group. An increased incidence of hepatocellular carcinomas was observed at 200 mg/kg/day and an increase in hepatocellular adenomas was seen at 60 and 200 mg/kg/day. The dose of 200 mg/kg/day produced a plasma AUC (0-24) value approximately 37 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug exposure after a 40 mg dose at steady state. An increased incidence of hepatocellular tumors was not seen at 10 mg/kg/day. The 60 mg/kg/day dose produced a plasma AUC (0-24) value approximately 4.9 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug exposure after a 40 mg dose at steady state. These hepatocellular effects are known to occur in rodents treated with statins without evidence of similar effects in humans.
Carcinogenicity	In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60 or 80 mg/kg/day, the incidence of uterine polyps was statistically significantly increased only in females at the dose of 80 mg/kg/day. This dose produced a plasma AUC (0-24) value approximately 8 times higher (after correction for interspecies differences in protein binding) than the human plasma drug exposure after a 40 mg dose at steady-state. Increased incidences of polyps observed at 2, 20 and 60 mg/kg/day were not statistically different from the control group not exposed to Rosuvastatin. The 60 mg/kg/day dose produced a plasma AUC (0 -24) value approximately 5 times higher (after correction for interspecies differences in protein binding) than the mean human exposure after a 40 mg dose at steady-state. The occurrence of uterine polyps in old female rats is well-known and is considered benign tumors and lesions termed non-neoplastic in humans. In a 107-week carcinogenicity study in mice given 10, 60, 200 or 400 mg/kg/day, the 400 mg/kg/day dose was poorly tolerated, resulting in early termination of this dose group. An increased incidence of hepatocellular carcinomas was observed at 200 mg/kg/day and an increase in hepatocellular adenomas was seen at 60 and 200 mg/kg/day. The dose of 200 mg/kg/day produced a plasma AUC (0-24) value approximately 37 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug

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SUMMARY OF HAZARD IDENTIFICATION:	
	exposure after a 40 mg dose at steady state. An increased incidence of hepatocellular tumors was not seen at 10 mg/kg/day. The 60 mg/kg/day dose produced a plasma AUC (0-24) value approximately 4.9 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug exposure after a 40 mg dose at steady state. These hepatocellular effects are known to occur in rodents treated with statins without evidence of similar effects in humans.
In vivo/In vitro Genotoxicity Studies	In vitro, Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with Salmonella typhimurium and Escherichia coli, L-5178 y ± mouse lymphomas and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the in vivo mouse micronucleus test.
Reproductive/Developmental Toxicity	**Pregnancy Category X:** Rosuvastatin is contraindicated in women who are or may become pregnant. Rosuvastatin may cause fetal harm when administered to a pregnant woman. **Teratology and Reproductive Studies:** The reproductive toxicity of Rosuvastatin has been evaluated in fertility and pre- and post-natal developmental studies, at doses up to 50 mg/kg/day. Slight reductions in maternal body weight gain and food consumption were observed at 50 mg/kg/day. Rosuvastatin had no adverse effects on mating, fertility in both sexes, implantation and maintenance of pregnancy, pup morphology or survival at 50 mg/kg/day in the fertility study. In a pre- and post-natal sighting study in rats given ≥ 75 mg/kg/day there was reduced pup survival at birth at 125 and 150 mg/kg/day and during early lactation at 75 and 100 mg/kg/day. In the main pre- and post-natal developmental study, Rosuvastatin showed no adverse effects on the duration of pregnancy, delivery and lactation in the dams in either generation at the high dose of 50 mg/kg/day. In the absence of plasma AUC exposure data in pregnant rats, comparisons with human data have been made on a received dose basis. The dose of 50 mg/kg/day equates to 90 times the human dose of 40 mg given to a 70 kg human. The potential of Rosuvastatin to cause developmental toxicity has been examined in the pregnant rat at doses up to 100 mg/kg/day and in the pregnant rabbit at doses up to 3 mg/kg/day. Rosuvastatin was shown to be neither embryo-fetolethal nor teratogenic in rats. At a maternally toxic dose of 3 mg/kg/day in rabbits, fetal examination showed no evidence of feto lethality or teratogenicity. Overall, Rosuvastatin has shown no reproductive or developmental toxicity.
Highly Sensitizing Potential	An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors. This has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA),

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SUMMARY OF HAZARD IDENTIFICATION:	
	erythrocyte sedimentation rate (ESR) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis and erythema multiforme including Stevens-Johnson syndrome.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No any adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effects	**Clinical Therapeutic Dose:** Initial Dose: 5 mg once daily. Maximum daily dose: 40 mg. **Adverse Effects:** Common side effects include abdominal pain, nausea, headaches and muscle pains. Serious side effects may include rhabdomyolysis, liver problems and diabetes. Use during pregnancy may harm the baby.

NOAEL/LOAEL	0.1 mg/kg/day value considered as NOAEL (Minimum daily dose)

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	5	For extrapolation from rats to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	1	107 weeks study available on rats.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.1 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$ = 0.02 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Rosuvastatin
- https://www.labriva.com/monographies/02380056eng.pdf
- https://pubchem.ncbi.nlm.nih.gov/compound/Rosuvastatin#section=Human-Metabolite-Information