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Steady-State Pharmacokinetics of Fluvastatin in Healthy Subjects Following a New Extended Release Fluvastatin Tablet, Lescol® XL†

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ABSTRACT: This was an open-label, randomized, three-period, three-treatment, multiple dose, crossover study in 12 healthy male and female subjects. This study evaluated single dose and steady-state pharmacokinetics of fluvastatin following single and multiple dose administrations of a new extended release fluvastatin 8 h matrix tablet, Lescol® XL 80 mg and 160 mg doses once a day. The study also included a twice a day administration of an immediate release (IR) form of fluvastatin capsule, Lescol®, for comparative purposes. All doses were administered for 7 days. The safety and tolerability were also assessed. The pharmacokinetics of fluvastatin were evaluated on days 1 and 7 following each treatment. Fluvastatin systemic exposure was 50% less when administered as Lescol® XL 80 mg qd compared with Lescol® IR 40 mg bid. Conversely, fluvastatin systemic exposure was 22% higher when administered as Lescol® XL 160 mg qd compared with Lescol® IR 40 mg bid. Single doses of Lescol® XL 80 mg and 160 mg were dose proportional but, deviation (30%) from dose proportionality was observed for the Lescol® XL 160 mg at steady-state. There appeared to be moderate (20%–40%) accumulation of serum fluvastatin maximal concentrations and exposure after multiple doses of Lescol® XL tablets. Both Lescol® XL 80 mg and 160 mg showed delayed absorption and longer apparent elimination half-life compared with fluvastatin IR capsule. Single and multiple doses of fluvastatin were generally well tolerated in this healthy volunteer population. Adverse event profiles were consistent with the published safety profile of the marketed formulations. Aside from one incidence of creatine phosphokinase (CPK) elevation (following Lescol® XL 160 mg qd treatment), there were no safety concerns with any of the treatments when administered acutely (7 days). Copyright © 2004 John Wiley & Sons, Ltd.

Key words: fluvastatin; extended-release; pharmacokinetics; hypocholesterolaemia

Introduction

Fluvastatin sodium (Lescol®) is a potent synthetic competitive reversible inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis in liver [1]. Lescol® is commercially available as an immediate release (IR) capsule or as an extended release 8 h 80 mg matrix tablet, Lescol® XL. Fluvastatin is effective in reducing lipids in patients with primary hypercholesterolaemia and mixed dyslipidaemia, i.e. Fredrickson Type IIa and IIb [2]. Doses of 20 to 80 mg/day of fluvastatin reduce total cholesterol, low density lipoprotein cholesterol and triglycerides and increase levels of high density lipoprotein cholesterol [3]. In addition to its lipid modulating

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effects, evidence now suggests that fluvastatin has antiarherogenic effects, which may be independent of its lipid-lowering properties that prevent coronary heart disease [2,4,5].

The pharmacokinetic properties of fluvastatin are well established [6–12]. After single doses, fluvastatin is almost completely (>90%) and rapidly absorbed with the time to maximum concentration occurring about 0.5 to 1.5 h post dose following oral dosing of the IR capsule form. Orally administered fluvastatin has low bioavailability (about 19% with a 2 mg dose to 29% with a 10 mg dose) due to its extensive first pass metabolism. Fluvastatin is highly bound to plasma proteins (>98%), over a plasma concentration range of 25 to 50,000 μg/ml. The steady-state volume of distribution of fluvastatin is 0.42 l/kg. More than 95% of the fluvastatin dose is metabolized by the liver. Excretion of fluvastatin and its metabolites is primarily by the biliary/faecal route with about 5% of the dose being excreted renally. The mean terminal half-life of fluvastatin following a single oral dose of the IR capsule, intravenous doses and multiple oral doses is 0.5 to 1 h. Exposure to fluvastatin is dose proportional up to 20 mg after a single oral dose of the IR capsule but showed 30%–40% deviation from dose proportionality at the 40 mg and 80 mg dose [9,13]. Saturation of the first pass metabolism of fluvastatin is probably responsible for the dose dependent increases in exposure to fluvastatin.

Adverse events associated with fluvastatin IR administration are generally mild and transient [2,3,14]. Headache, dyspepsia, diarrhoea, abdominal pain, nausea and insomnia are the most frequently reported side effects. Asymptomatic increases in hepatic transaminases and creatine phosphokinase concentrations have also been observed following fluvastatin IR administration.

An extended release matrix formulation of fluvastatin (Lescol® XL) 80 mg provides sustained release of fluvastatin over 8 h resulting in lower fluvastatin systemic concentrations. Additionally, the 80 mg Lescol® XL tablet is administered once a day in contrast to twice a day administration of 40 mg Lescol® IR capsule. Thus, the XL tablet could improve patient compliance. Extended release of fluvastatin would also be expected to have a more efficient hepatic uptake and avoid saturation of first pass hepatic metabolism. Additionally, the slow release formulation would result in lower systemic drug concentrations and exposure which may result in a lower incidence of systemic adverse events when compared with the IR formulation. The clinical safety is well established for both the fluvastatin IR formulation (40 mg capsule bid) and the Lescol® XL formulation (80 mg tablet qd) in patients with primary hypercholesterolaemia and mixed dyslipidaemia [15]. Lescol® XL 80 mg offers enhanced efficacy compared with fluvastatin IR 40 mg in reducing total cholesterol, LDL (−38%) and triglycerides (up to −31%) and increasing HDL (+21%).

The goal of the present study was to characterize the multiple dose steady-state pharmacokinetics of the currently marketed 8 h matrix tablet, Lescol® XL, at doses of 80 mg or 160 mg administered once a day for 7 days to healthy subjects and to compare its pharmacokinetics with Lescol® IR 40 mg capsules administered twice a day for 7 days. The safety and tolerability of multiple dose administrations of Lescol® XL and Lescol® IR also were assessed.

Materials and Methods

Study design

This was an open-label, randomized, three-period, three-treatment, multiple dose, crossover study in healthy male and female subjects. Each subject received one 80 mg Lescol® XL tablet once daily (total 80 mg/day) or two 80 mg Lescol® XL tablets once daily (total 160 mg/day), or one 40 mg fluvastatin IR Lescol® capsule twice daily (q 12 h; total 80 mg/day) as per the randomization schedule for 7 days. There was a 3-day interdose interval (washout) between treatments.

On study days 1 and 7, the study medications were administered in the study center with 200 ml of water after a 10-h fast. The day 2 morning dose was given at the study centre, and then the subjects received study medication on an outpatient basis from day 2 to day 6. All subjects continued to fast for at least 4 h post dose. The intake of xanthine (e.g. caffeine)

containing food or beverages, alcohol and strenuous physical exercise were restricted before dosing until after the study completion.

Except for medication required to treat adverse events, no medication other than the study drug was allowed from 14 days prior to dosing until all of the final study evaluations had been completed. Administration of acetaminophen (paracetamol) was acceptable as needed.

This study was performed in accordance with the Declaration of Helsinki ('Recommendations Guiding Physicians in Biomedical Research Involving Human Patients', Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996), the Rules Governing Medicinal Products in the European Community (Directive 91/507/EEC), and the US Code of Federal Regulations dealing with clinical studies concerning Informed Patient Consent and IRB approval.

Study population

Twelve healthy male and female subjects between the ages of 18 and 45 and within 15% of ideal body weight were enrolled in the study. Female subjects were using either double barrier contraception, were post-menopausal or were surgically sterile. Subjects were in good health as determined by past medical history, physical examination, vital signs, electrocardiogram and laboratory tests (haematology, biochemistry and urinalysis) at screening. All subjects were non-smokers.

The assessment of background and demographic data included medical history, current medical conditions, date of birth, sex, race, height, elbow breadth and frame size. Subjects were screened for drugs of abuse (e.g. alcohol, benzodiazepines, amphetamines, cannabinoids, cocaine and opiates), hepatitis B and C, HIV, cotinine and pregnancy in female subjects.

Safety assessments

Safety assessments included the monitoring and recording of all observed or reported adverse events, regular checks of routine blood chemistry, haematology and urine values, ECG recordings, measurements of vital signs and physical examinations.

Pharmacokinetic assessments

Five millilitres (ml) of venous blood was drawn from the subject's forearm vein to determine fluvastatin serum concentrations following each Lescol® XL treatment at the following times on days 1 and 7: predose (0 h), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post dose. Following fluvastatin IR treatment, blood samples were collected at the following times on days 1 and 7: predose (0 h), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 12.5, 13, 14, 16, 20 and 24 h post morning dose. Blood samples were drawn into red-stoppered, SST® serum separation tubes and placed at room temperature protected from direct sunlight and UV irradiation. After 15 min, the samples were centrifuged at between 3°C and 5°C for at least 15 min at approximately $800 \times \mathbf{g}$. The serum was separated into polypropylene screw-cap tubes and samples were frozen at $\leqslant -20$°C for drug analysis.

Drug analysis

Serum concentrations of fluvastatin were quantitated using a high performance liquid chromatographic method with fluorescence detection. The limit of quantitation was 2.0 ng/ml. The assay was validated within a concentration range of 4–400 ng/ml. The accuracy of the method within the range of 95.9%–107% and the precision, determined as the percent coefficient of variation, was within the range of 2.0%–9.3%, for calibration samples and 4.7%–19.0% for quality control samples.

Pharmacokinetic variables

Serum fluvastatin concentrations were used to determine the following pharmacokinetic parameters by non-compartmental methods using WinNonlin Pro Version 3.1 (Pharsight Corporation, Mountain View, CA): C_{max}: maximum concentration observed post dose; C_{min}: minimal concentration observed post dose; C_{24}: concentration observed at 24 h; t_{max}: time at which the C_{max} occurred; AUC_{0-t}: area under the concentration-time curve (AUC) from time zero to the last measurable sampling time point (t),

calculated by linear trapezoidal method; $AUC_{0-\infty}$: $AUC_{0-t} + C_t/\lambda_z$, where C_t is the concentration at time t, and λ_z is the terminal elimination rate constant; AUC_τ:AUC in a dosing interval at steady-state; $t_{\frac{1}{2}}$: elimination half-life, determined as $0.693/\lambda_z$; C_{max}/AUC_{0-t}: used as a surrogate measure for rate of absorption; C^{ss}_{av}: average concentration at steady-state calculated as AUC_τ/τ, where τ is a dosing interval; AF(C_{max}): Accumulation Factor based on C_{max} calculated as C^{ss}_{max}/C_{max}; AF(AUC): accumulation factor based on AUC calculated as AUC_τ/AUC_{0-t}; FI: fluctuation Index calculated as $(C^{ss}_{max} - C^{ss}_{min})/C^{ss}_{av}$.

Results

Study population

A total of 12 subjects, six Caucasians, five blacks and one of other racial origin were enrolled in the study and all 12 subjects completed all three treatment periods. Of the 12 subjects, eight were males and four were females. The mean ($\pm$ SD) age was 29 ($\pm$ 8) years and the mean ($\pm$ SD) height and weight were 172 ($\pm$ 7) cm and 70 ($\pm$10) kg, respectively.

Safety and tolerability

Adverse events were reported by six of 12 subjects after administration of study drugs. A total of 36 adverse events were reported (seven moderate and 29 mild) of which 20 episodes followed Lescol® XL 80 mg qd (four moderate and 16 mild); four episodes followed Lescol® XL 160 mg qd (two moderate and 2 mild); and 12 episodes followed fluvastatin 40 mg bid (one moderate and 11 mild). The most common adverse events were headache (eleven episodes), fatigue (five episodes), and nausea (three episodes). Of the 36 adverse event episodes reported, only two episodes (one each of fatigue and nausea) were suspected to be study drug related. Both were mild and in the same subject on the same day following fluvastatin IR 40 mg bid. Acetaminophen was the only concomitantly administered medication for the treatment of headaches.

A clinically meaningful elevation in creatine phosphokinase (CPK) of 2265 IU/l was observed in one subject at study completion (most recent treatment was Lescol® XL 160 mg qd). As the subject did not report increased physical activity, it is unlikely that the observed increase in CPK measurements was related to physical activity. This subject did not report any other symptoms and had normal renal function. Four days following the last dose of study drug, the CPK value was similar to those observed at screening and baseline (289 IU/l and 234 IU/l, respectively).

Another subject had an alanine transferase value of 247 IU/l and an aspartate transferase value of 198 IU/l at study completion (most recent treatment was fluvastatin IR 40 mg bid). At a subsequent follow-up visit ($\sim$18 days post last dose), these values were 19.0 IU/l and 24.0 IU/l, respectively.

Vital sign assessments, physical examinations and clinical laboratory results revealed no trends of concern.

Pharmacokinetic results

The fluvastatin concentrations for one subject could not be determined due to the presence of interfering peaks during the sample analysis for all the three treatments on day 7. Thus, data from only 11 subjects was available for pharmacokinetic analysis on day 7.

Pharmacokinetics following single dose (day 1). The mean serum concentration versus time plots for fluvastatin are presented in Figure 1. Following the administration of Lescol® XL, the serum fluvastatin concentrations increased gradually reaching maximum levels at about 4 h. With the fluvastatin IR first dose, the serum fluvastatin concentration increased rapidly reaching maximum levels within 1 h. Following the second dose of fluvastatin IR, the maximum serum fluvastatin concentration were reduced compared with the first dose. There appeared to be a delay in the time to maximum concentrations.

The mean pharmacokinetic parameters of fluvastatin following a single dose are summarized in Table 1. Fluvastatin was absorbed quickly with a median (range) t_{max} of 0.5 (0.5–1) h

following fluvastatin IR capsules and the absorption was delayed following Lescol® XL tablets to 2.5–3.0 (1.5–8) h. The mean C_{max} was about 4-fold higher when subjects received fluvastatin IR 40 mg bid compared with Lescol® XL 80 mg qd. Following the Lescol® XL 160 mg qd dosing, the C_{max} was 2-fold higher compared with Lescol® XL 80 mg qd dose. The exposure to fluvastatin, as measured by AUC_{0-t}, was about 2-fold higher with fluvastatin IR 40 mg bid compared with Lescol® XL 80 mg qd but similar to Lescol® XL 160 mg qd dose. The $AUC_{0-\infty}$ could not be calculated in all subjects within each treatment due to limitations of determining λ_z values.

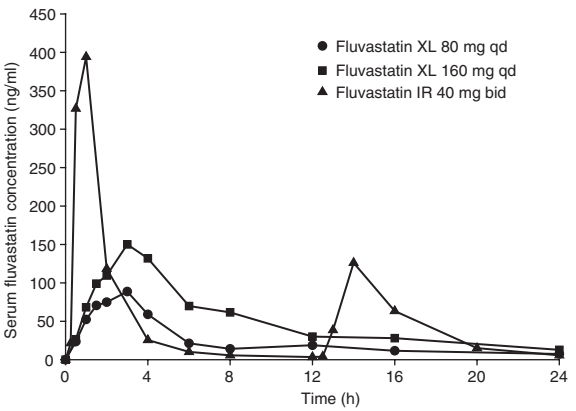

Figure 1. Mean serum concentrations of fluvastatin following single oral doses (day 1) of Lescol® XL 80 mg qd, Lescol® XL 160 mg qd, and fluvastatin IR 40 mg bid in 12 healthy subjects

Although $t_{\frac{1}{2}}$ values were not available in all subjects, a prolongation of the apparent $t_{\frac{1}{2}}$ was observed following the Lescol® XL tablets compared with fluvastatin IR capsules. The ratio of C_{max}/AUC_{0-t}, a surrogate measure for the rate of absorption, was similar for Lescol® XL 80 and 160 mg but approximately 50% of that for fluvastatin IR 40 mg bid.

Pharmacokinetics following multiple doses (day 7). Following multiple dosing for 7 days, the rise and decline in serum fluvastatin concentration profiles was similar to that seen following a single dose for all the treatments (Figure 2). The serum concentrations of fluvastatin were higher with the Lescol® XL 160 qd multiple dosing compared with that of the single dose. As with the single dose, reduced fluvastatin concentrations following the second dose of fluvastatin IR as well as a delay in t_{max} were also observed with multiple dose administration of IR.

Steady-state conditions following 7 days of administration of Lescol® XL tablets or fluvastatin IR capsules were achieved as assessed by similar fluvastatin serum concentrations at predose and at 24 h postdose on day 7. In addition, serum concentrations at 12 h were judged to be close to predose and 24 hour post dose for the fluvastatin IR 40 mg bid supporting steady-state conditions. (Table 2).

Fluvastatin was absorbed quickly with a median (range) t^{ss}_{max} of 1 (0.5–2) h following fluvastatin IR capsules and slightly delayed

Table 1. Mean (CV%) fluvastatin pharmacokinetic parameters following single oral doses (day 1) of Lescol® XL 80 mg qd, Lescol® XL 160 mg qd, and fluvastatin IR 40 mg bid in 12 healthy subjects

PK parameter	Mean (CV%)		
	Lescol XL 80 mg qd	Lescol XL 160 mg qd	Fluvastatin IR 40 mg bid
t_{max} (h)[a]	2.5 (1.5-4)	3.0 (1.5-8)	0.5 (0.5-1)
C_{max} (ng/ml)	101.5 (62)	209.5 (43)	438.4 (53)
C_{24} (ng/ml)	7.75 (110)	12.8 (59)	9.22 (97)
AUC_{0-t} (ng*h/ml)	564 (64)	1201 (46)	1165 (48)
$AUC_{0-\infty}$ (ng*h/ml)	1017[b] (81)	1151[c] (49)	1125[d] (46)
$t_{\frac{1}{2}}$ (h)	10.5[b] (46)	7.7[c] (30)	2.3[d] (18)
C_{max}/AUC_{0-t}	0.19 (34)	0.18 (25)	0.37 (27)

[a] Median (range).
[b] n=4.
[c] n=8.
[d] n=10.

following Lescol® XL tablets to 2.0 to 3.0 (1–6) h. The exposure to fluvastatin, as measured by AUC_τ, was about 2.1-fold in subjects when receiving fluvastatin IR 40 mg bid compared with Lescol® XL 80 mg qd. Following the Lescol® XL 160 mg qd dosing, the fluvastatin exposure was 2.7-fold compared with Lescol® XL 80 mg qd dose. As with a single dose, a trend towards prolongation of the $t_{\frac{1}{2}}$ was observed following the Lescol® XL tablets compared with the fluvastatin IR capsules. Also the ratio of C^{ss}_{max}/AUC_τ was similar to the single dose.

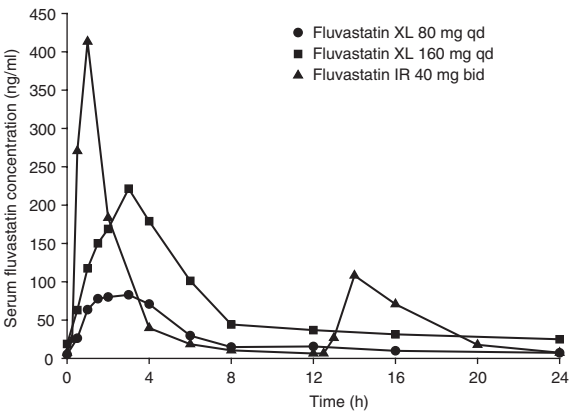

Figure 2. Mean serum concentrations of fluvastatin following multiple oral doses (day 7) of Lescol® XL 80 mg qd, Lescol® XL 160 mg qd, and fluvastatin IR 40 mg bid in 11 healthy subjects

The accumulation factor based on C_{max}, AF(C_{max}), was similar for the XL tablets and the IR capsule (1.2–1.4). Similarly, the accumulation factor based on AUC, AF(AUC), was 1.2 for the fluvastatin IR 40 mg bid and 1.3 and 1.4 following Lescol® XL 80 mg qd, and Lescol® XL 160 mg qd, respectively. The fluctuation index was similar at 3.9 and 3.8 for the Lescol® XL 80 mg qd and Lescol® XL 160 mg qd, respectively. The fluctuation index for fluvastatin IR 40 mg bid was 7.9. As expected, the fluctuation index was higher for fluvastatin IR than Lescol® XL due to a greater C_{max} of the IR capsule.

Discussion

The Lescol® XL 80 mg matrix tablet is currently a marketed product and this study characterized the steady-state pharmacokinetics of fluvastatin following the Lescol® XL tablets and compared the steady-state pharmacokinetics with the marketed fluvastatin IR capsules.

The pharmacokinetic parameters of fluvastatin IR in this study are in agreement with those published previously following 40 mg and 80 mg doses [6,8,9,13]. To date, pharmacokinetic parameters of a fluvastatin 12 h extended release matrix tablet have been reported only in one study in which single and multiple 80 mg to 640 mg doses were administered to patients with

Table 2. Mean (CV%) fluvastatin pharmacokinetic parameters following multiple oral doses (day 7) of Lescol® XL 80 mg qd, Lescol® XL 160 mg qd, and fluvastatin IR 40 mg bid in 11 healthy subjects

PK parameter	Mean (CV%)		
	Lescol XL 80 mg qd	Lescol XL 160 mg qd	Fluvastatin IR 40 mg bid
t^{ss}_{max} (h)[a]	2.0 (1-4)	3.0 (1.5-6)	1.0 (0.5-2)
C^{ss}_{max} (ng/ml)	102.4 (41)	258.8 (43)	442.8 (43)
C^{ss}_{min} (ng/ml)	7.71 (58)	25.3 (124)	9.19 (49)
AUC_τ (ng*h/ml)	630 (52)	1704 (64)	1340 (41)
$t_{\frac{1}{2}}$ (h)	8.8[b] (72)	7.3[c] (35)	2.8[d] (48)
C^{ss}_{max}/AUC_τ	0.17 (30)	0.18 (37)	0.34 (39)
AF(C_{max})	1.2 (48)	1.3 (42)	1.4 (98)
AF(AUC)	1.3 (34)	1.4 (49)	1.2 (36)
FI	3.9 (33)	3.8 (46)	7.9 (39)

[a] Median (range).
[b] n=6.
[c] n=5.
[d] n=10.

primary hypercholesterolaemia [16]. The extended release formulation used in the previous study was a 12 h release, whereas the XL tablet used in the present study was an 8 h release. Generally, the maximum concentration and systemic exposure achieved in the previous study were 40%–50% lower for the Lescol® XL 80 mg tablet compared with this study. In the case of Lescol® XL 160 mg dose, a 20% lower maximum concentration was observed in the previous study but the systemic exposure was quite similar between the two studies. The difference observed between the two studies could be attributed to differences in formulations (release rates) and types of subjects (healthy subjects in the present study versus patients with hypercholesterolaemia in the previous study). It has been previously documented that the maximum concentration and exposure to fluvastatin following similar fluvastatin IR doses were lower in patients with hypercholesterolaemia compared with healthy subjects [9]. Although age was found not to effect the pharmacokinetics of fluvastatin [7,11], an effect of gender on the pharmacokinetics of fluvastatin has been observed [7,11,17].

Following single and multiple doses, the absorption of fluvastatin was delayed by about 1–2 h with Lescol® XL compared with fluvastatin IR. The absorption rate, as measured by C_{max}/AUC_{0-t}, was 50% lower for Lescol® XL than for fluvastatin IR. This was expected from the extended release and immediate release dosage forms. The serum fluvastatin concentrations for the Lescol® XL tablets were much lower compared with the fluvastatin IR capsules. The systemic exposure to fluvastatin following the same total dose over 24 h period (fluvastatin IR 40 mg bid and Lescol® XL 80 mg qd) was about 2-fold lower when subjects received Lescol® XL 80 mg qd compared with fluvastatin IR 40 mg bid following single and multiple doses. Following Lescol® XL 160 mg qd, the exposure was only 22% higher compared with fluvastatin IR 40 mg bid. Fluvastatin is known to undergo extensive first pass metabolism that is dose-dependent [10] due to saturation of the metabolic enzymes during the absorption phase. The bioavailability of fluvastatin following oral doses ranged from 20% (at 2–5 mg dose) to 50% at 40 mg. Thus lower exposure following the extended release tablets could be due to the efficient first pass uptake of the drug as a result of slower and sustained drug release.

The half-life of fluvastatin following Lescol® XL was longer compared with fluvastatin IR administration following single and multiple doses (mean range 7.3–10.5 h versus 2.3–2.8 h, respectively). Following administration of fluvastatin either intravenously or orally, the half-lives were found to be similar [16] and ranged from 0.5–2.6 h [11]. Consequently, it appears that the longer half-life (sustained serum concentrations) observed with Lescol® XL represents prolonged absorption.

Following single doses of Lescol® XL 80 mg and 160 mg, a 2-fold increase in dose, a doubling of the maximum concentration and exposure was observed. Thus, following single doses, the Lescol® XL 80 and 160 mg doses were dose proportional. At steady-state, a 2.5-fold increase in maximum concentration and a 2.7-fold increase in exposure was observed with the doubling of dose with no changes in the dose independent pharmacokinetic parameters. This indicates a (30%) deviation from dose proportionality at steady-state and may be due to a trend towards saturable first pass metabolism [10]. Since the C_{max}/AUC ratios were similar after both Lescol® XL 80 mg and 160 mg single and multiple doses, it appears that the absorption rate was unchanged with Lescol® XL tablets up to 160 mg.

The pharmacokinetic parameters of fluvastatin following a single administration of fluvastatin IR 40 mg bid were similar to that observed following multiple administrations (7 days), indicating that the absorption and elimination of fluvastatin IR were similar following single and multiple doses. Following single and multiple doses of fluvastatin IR, the serum concentrations of fluvastatin after the second dose of fluvastatin IR during bid dosing were lower than that after the first dose. The most likely explanation for this phenomenon is a reduced exposure due to the effect of food as the evening meal was provided to the subjects 3 h before the second daily dose [7,11]. A reduction of up to 74% in maximum concentration and up to 44% in systemic exposure was observed when

fluvastatin was administered as the IR capsule with food ranging from a high fat meal to only carbonated beverages. A delay in the time to maximum absorption was also observed. This food effect was evident even when Lescol® IR administration occurred 4 h after a meal [7]. The rate of bioavailability of fluvastatin is not, however, a determinant of its effect. Food appears to decrease the bioavailability of fluvastatin but does not alter its hypocholesterolaemic efficacy [14]. Another study conducted in patients with hypercholesterolaemia, showed that food did not significantly affect the extent of absorption of fluvastatin IR and that the efficacy and tolerability following fluvastatin 20 mg/day for 16 weeks was the same following administration with the evening meal versus administration at bed time [3].

The accumulation factor was calculated using both the maximum concentration and systemic exposure. Fluvastatin showed some accumulation following multiple dosing for 7 days. The accumulation of fluvastatin was similar for the fluvastatin IR and XL dosing (approximately 20% to 40%). Previous studies have indicated that fluvastatin does not accumulate following Lescol® IR multiple dosing but there was some accumulation following Lescol® XL multiple dosing. The moderate accumulation of fluvastatin (AF(C_{max})) with Lescol® IR 40 mg bid was mostly due to one subject, however, the mean AF(C_{max}) of the remaining subjects was approximately 1.0, indicating no accumulation on average.

The safety and tolerability of fluvastatin doses up to 80 mg/day has been well characterized in previous studies [3,15]. One subject did present with clinically meaningful elevations in CPK measurements following 7 days of Lescol® XL 160 mg treatment. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in CPK values to greater than 10 times the upper limit of normal, has been reported with fluvastatin and with other drugs in this class. As the CPK elevation was not accompanied with muscle pain or reduced renal function this elevation was not attributed to drug treatment. Most adverse events reported during this study were not study drug related. There were only two adverse events that were considered study drug related and both followed the fluvastatin IR 40 mg bid dose. Both these adverse events resolved spontaneously. With the exception of one incidence of CPK elevation there were no clinical safety concerns with any of the three treatments. Overall, the fluvastatin was well tolerated by healthy subjects, whether given as Lescol® XL 80 mg or 160 mg once-a-day or Lescol® IR 40 mg 12 h.

In conclusion, following administration of Lescol® IR capsules 40 mg bid or Lescol® XL 80 mg qd or Lescol® XL 160 mg qd for 7 days, the pharmacokinetics of fluvastatin were similar between single dose and multiple doses. Lescol® XL 80 mg qd showed lower serum drug exposure, whereas Lescol® XL 160 mg qd showed slightly higher serum drug exposure compared with fluvastatin IR 40 mg bid. Single and multiple doses of fluvastatin were generally well tolerated in this healthy volunteer population. Adverse event profiles were consistent with the published safety profile of the marketed formulations. Aside from one incidence of CPK elevation, there were no safety concerns with any of the treatments when administered acutely (7 days).

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