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ADIS DRUG EVALUATION

Pitavastatin: A Review in Hypercholesterolemia

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Abstract Oral pitavastatin (Livalo®; Livazo®) is a competitive HMG-CoA reductase inhibitor that is available in the EU for the reduction of elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels in adults with primary hypercholesterolemia and combined (mixed) dyslipidemia. In short-term, phase III or IV studies in this patient population, pitavastatin 1–4 mg once daily was generally no less effective than presumed equipotent dosages of atorvastatin and simvastatin (including in patients with type 2 diabetes or ≥2 cardiovascular risk factors) and was superior to pravastatin (including in patients aged ≥65 years) in lowering LDL-C levels. Pitavastatin provided sustained LDL-C-lowering efficacy over up to 60 weeks' therapy in extension studies, and was associated with short- and longer-term improvements in several other lipid parameters. Short- and longer-term outcomes in studies in Asian patients were consistent with these findings. Pitavastatin was generally well tolerated and did not appear to adversely affect glucose metabolism parameters (e.g. fasting blood glucose, fasting plasma glucose, fasting plasma insulin, glycated hemoglobin) in short- and longer-term prospective and post-marketing surveillance studies in adults. Moreover, in combination with lifestyle modification advice, it was associated with a significant reduction in the risk of progression from impaired glucose tolerance to diabetes relative to lifestyle modification advice alone in a longer-term study in Japanese subjects. Thus, pitavastatin is an effective treatment option in adults with primary hypercholesterolemia and combined (mixed) dyslipidemia, including those at risk of developing type 2 diabetes.

Pitavastatin: clinical considerations in hypercholesterolemia
Generally no less effective than presumed equipotent dosages of atorvastatin and simvastatin and superior to pravastatin in lowering LDL-C levels, and associated with improvements in other lipid parameters
Benefits maintained during longer-term treatment
Does not appear to adversely affect glucose metabolism parameters or the risk of developing diabetes. No confirmed signal of a diabetes risk in prospective studies or post-marketing safety surveillance studies
Generally well tolerated, with most treatment-emergent adverse events mild or moderate

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1 Introduction

Cardiovascular disease (CVD) risk most commonly results from multiple interacting risk factors [1]. CVD prevention requires a multifaceted approach aimed at minimizing or eliminating the impact of CVD and its associated

disability. Guidance should be given to both the general population (by promoting healthy lifestyle behavior) and to individual patients with moderate to high CVD risk or established CVD [by addressing an unhealthy lifestyle (e.g. poor diet, physical inactivity, smoking) and reducing elevated cardiovascular risk factor levels (e.g. elevated blood pressure and lipid levels)], with the actions in individuals tailored to their total risk (i.e. the higher the risk, the more intense the action should be) [1]. These risk factors are also risk factors for type 2 diabetes, which is itself a risk factor for CVD [1, 2].

There is considerable evidence that lowering lipid levels, particularly low-density lipoprotein cholesterol (LDL-C) levels, reduces the risk of CVD [1, 3], with HMG-CoA reductase inhibitors (hereafter known as statins) the mainstay of pharmacotherapy [4]. Statins as a class have been shown to increase the risk of dysglycemia and the development of type 2 diabetes, although this risk is outweighed by the reduction in CVD risk [1, 4]; recent research has focused on elucidating the potential for individual statins, including pitavastatin, to increase the risk of developing diabetes.

This article provides an updated narrative review of pharmacological, therapeutic efficacy and tolerability data relevant to the oral use of pitavastatin (Livalo®; Livazo®) [including data pertaining to the effects on glucose metabolism and the risk of developing type 2 diabetes] in adults with primary hypercholesterolemia or combined (mixed) dyslipidemia, with a focus on the EU label. Discussion of the use of pitavastatin in children, or in adults with HIV is beyond the scope of this review.

2 Pharmacological Properties of Pitavastatin

The pharmacological properties of pitavastatin are well established and have been reviewed previously [5]; therefore, this section provides a brief overview.

2.1 Pharmacodynamic Profile

Pitavastatin is a competitive inhibitor of HMG-CoA reductase [6]. Inhibiting this (rate-limiting) enzyme impedes cholesterol synthesis in the liver, thereby increasing LDL-C receptor expression and subsequently the uptake of circulating LDL from the blood, which in turn reduces LDL-C (dose dependently [7]) and total cholesterol levels [6]. Moreover, sustained cholesterol synthesis inhibition in the liver reduces blood very-low density lipoprotein cholesterol levels, thereby reducing plasma triglyceride levels [6]. In vitro, pitavastatin competitively inhibited HMG-CoA reductase [with a median (50%) inhibitory concentration of 6.8 nmol/L and an inhibitory affinity constant of 1.7 nmol/L] 2.4- and 6.8-fold more potently than simvastatin and pravastatin [8]. Pitavastatin also attenuated abnormalities in the plasma lipidome of 12 adults with mixed dyslipidemia and metabolic syndrome participating in a 24-week study [9] (see Sect. 6).

The mechanism by which statins affect glucose homeostasis is not fully understood [10]. It has been postulated that statins increase plasma glucose levels and the risk of developing new-onset diabetes via reduced HMG-CoA reductase activity, increased insulin resistance and/or impaired β-cell function [10]. In vitro, atorvastatin, pravastatin, rosuvastatin and pitavastatin (each at concentrations of 100 nmol/L) exhibited a cytotoxic effect on human pancreas islet β cells, with reductions in cell viability of 32, 41, 34 and 29%, respectively, versus control [11]. This effect was dose-dependent (i.e. at lower doses there was a lesser cytotoxic effect). Moreover, insulin secretion rates were decreased by 34, 30, 27 and 19%, respectively, relative to control. In human skeletal muscle cells, glucose uptake rates were 59, 60, 73 and 90% with atorvastatin, pravastatin, rosuvastatin and pitavastatin (each at concentrations of 100 nmol/L) [11]. Pitavastatin appeared to improve postprandial oxidative stress, according to a study in Japanese men with abdominal obesity, but did not affect glucose, insulin or high-sensitivity C-reactive protein levels [12]. Pitavastatin may exert an adiponectin-dependent anti-atherosclerotic effect, with a study in patients with hyperlipidemia and type 2 diabetes demonstrating a significant ($p < 0.01$) increase from baseline in adiponectin levels following 3 and 6 months' therapy with pitavastatin [13]. Adiponectin levels are inversely related to visceral obesity and insulin resistance, with high adiponectin levels associated with a substantially reduced risk of type 2 diabetes [10]. By inhibiting HMG-CoA reductase and thus the mevalonate pathway, statins reduce various downstream products, including coenzyme Q10 (CoQ10; ubiquinone), thereby impairing the production of ATP, which is an essential regulator of insulin secretion [10, 14]. In a 12-week, randomized, double-blind study in 134 patients with impaired glucose tolerance (IGT), pitavastatin 4 mg once daily decreased plasma ubiquinol levels from baseline by a significantly ($p < 0.05$) lesser extent than atorvastatin 20 mg once daily and rosuvastatin 5 mg once daily [15]. No significant between-group differences in the reduction from baseline in plasma total Coenzyme Q10 and ubiquinone levels were seen [15]. The effects of pitavastatin on glucose metabolism parameters in patients participating in clinical studies are discussed in Sect. 4.1.

Other pleotropic effects exhibited by pitavastatin (and other statins) include those on atherosclerosis, cardiovascular function, inflammation, and platelets and platelet activation markers [5, 16, 17].

Pitavastatin (up to 16 mg/day) was not associated with clinically meaningful prolongation of the corrected QT interval or heart rate in healthy volunteers [18].

2.2 Pharmacokinetic Profile

Pitavastatin exhibited approximately dose-proportional area under the concentration–time curve (AUC) from time 0 to infinity and maximum concentration (C_{max}) values over a 1–24 mg dose range following single oral doses [18]. Pitavastatin was rapidly absorbed from the upper gastrointestinal tract after oral administration, with plasma C_{max} reached within 1 h and an absolute bioavailability of 51% [6, 18]. The absorption of pitavastatin is unaffected by food [6, 18] (Sect. 5). Plasma AUC values vary (with an ≈4-fold range seen between minimum and maximum values) between individuals [6]. Pitavastatin is highly bound (>99%) to proteins (mostly albumin and alpha 1-acid glycoprotein) in human plasma [6, 18]. The principal drug moiety in plasma is unchanged pitavastatin [6].

Pitavastatin is actively transported into hepatocytes (the site of action and metabolism) by multiple hepatic transporters (OATP1B1, OATP1B3, OATP2B1 and NTCP) [6, 19]. It is metabolized primarily via glucuronidation (mediated by UGT1A3 and UGT2B7) to form pitavastatin lactone (which is inactive) [6, 18]. Pitavastatin is minimally metabolized by cytochrome P450 (CYP)2C9, and to a lesser extent CYP2C8 [6, 18]. It is thought to be protected from CYP3A4 metabolism by the cyclopropyl moiety on its base structure [20]. P-glycoprotein (p-gp)-mediated transport does not play a major role in the disposition of pitavastatin [19], with pitavastatin not a substrate of P-gp [6].

The parent drug is rapidly cleared from the liver to the bile, although it does undergo enterohepatic circulation, thereby extending the duration of action of pitavastatin [6]. Less than 5% of pitavastatin is excreted in the urine. The plasma elimination half-life at steady state is 8.9 h. Following a single dose, the apparent mean oral clearance of pitavastatin is 43.4 L/h [6].

The pharmacokinetics of pitavastatin are not affected to any clinically relevant extent by factors such as patient age, ethnicity or sex [6, 18]. Exposure to pitavastatin was increased 1.6- and 3.9-fold in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, respectively, compared with healthy subjects [6] (see Sect. 5).

Pitavastatin appears to have a low potential for drug-drug interactions, according to post hoc analyses [21] of a post-marketing surveillance study (LIVES; $n = 19{,}925$) [22] [discussed in Sect. 3.2.1] and pooled data from five multinational, phase III studies ($n = 2396$) [23–27] [discussed in Sect. 3.1]. Like pravastatin and rosuvastatin, but unlike atorvastatin, fluvastatin, lovastatin and simvastatin, pitavastatin is not susceptible to CYP inhibition [28], with no clinically significant effect on plasma pitavastatin concentrations seen in interaction studies with known CYP3A4 inhibitors grapefruit juice and itraconazole [6]. Moreover, neither pitavastatin nor its metabolite (pitavastatin lactone) inhibit CYP [19]. However, pitavastatin is actively transported into hepatocytes by multiple hepatic transporters (although it appears to be less dependent on OATP1B1 transportation, with OATP1B1 inhibitors having a minimal effect on plasma pitavastatin concentrations [19]); therefore, interactions may occur with coadministered agents that are also transported via this route [6, 29]. Indeed, pitavastatin is contraindicated in patients receiving concomitant cyclosporine (Sect. 5) and should be discontinued during therapy with erythromycin and other macrolide antibacterials, as exposure to pitavastatin may be increased [6]. Moreover, pitavastatin must not be coadministered during and within 7 days of discontinuing systemic fusidic acid therapy and caution is advised when either fibrates or niacin are coadministered, as monotherapy with niacin and combination therapy with fibric acid derivatives or fusidic acid and statins have been associated with myopathy and/or rhabdomyolysis [6].

3 Therapeutic Efficacy of Pitavastatin

This section discusses the short-term (Sect. 3.1) and longer-term (Sect. 3.2) efficacy of oral pitavastatin in patients (including Asian patients) with primary hypercholesterolemia or combined (mixed) dyslipidemia.

3.1 Short-Term Therapy

Six large ($n > 325$), randomized, double-blind, double-dummy, active comparator-controlled, multinational [23–27] or multicentre [30], phase III [23–27] or IV [30] studies assessed the short-term efficacy of pitavastatin in patients (aged ≥18 years) with uncontrolled primary hypercholesterolemia or combined (mixed) dyslipidemia despite dietary measures. One study was conducted in patients aged ≥65 years [27], one in patients with concomitant type 2 diabetes [glycated hemoglobin (HbA_{1c}) ≤7.5%] (who received concomitant oral antidiabetic drug [not including glitazones] or insulin therapy) [24] and one in patients with ≥2 cardiovascular risk factors [25].

Across the studies, patients received pitavastatin 1, 2 or 4 mg or an active comparator (atorvastatin or simvastatin at a presumed equipotent dosage, or pravastatin at a dosage reflecting actual prescribing in the USA and Europe) once daily for 12 weeks [23–27, 30]. The primary endpoint was the percentage change in LDL-C levels from baseline to endpoint [23–27, 30]. The primary objective was to assess

the noninferiority [23–27] or superiority [30] of pitavastatin versus an active comparator in terms of the primary endpoint. Analyses were conducted in the full analysis set (FAS) [23–27] or intent-to-treat population [30].

Pitavastatin was generally no less effective than presumed equipotent dosages of atorvastatin and simvastatin [23–26] and was superior to pravastatin [27, 30] in terms of the primary endpoint (Table 1). While noninferiority was not demonstrated at week 12 between pitavastatin and atorvastatin in the study in patients with concomitant type 2 diabetes, clinically relevant improvements in LDL-C levels of over 40% were observed in both treatment groups (Table 1). Over half of the patients receiving pitavastatin or a comparator statin in the noninferiority trials achieved target LDL-C levels set by the National Cholesterol Education Program (NCEP) Adult Treatment Plan (ATP) III and the European Atherosclerosis Society (EAS) [Table 1]. In the superiority study [30], significantly ($p < 0.001$) more pitavastatin 4 mg once daily than pravastatin 40 mg once daily recipients achieved LDL-C levels of <100 mg/dL (47.2 vs. 12.4%) and <130 mg/dL (82.0 vs. 61.5%). No significant between-group differences were observed in the proportions of patients achieving LDL-C levels of <160 mg/dL or <70 mg/dL [30].

Short-term therapy with pitavastatin demonstrated beneficial effects on other lipid parameters. There were generally no significant differences in the changes in total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglyceride levels between pitavastatin and atorvastatin, pravastatin or simvastatin (Table 1) and in the changes in non-HDL-C levels and non-HDL-C : HDL-C and total cholesterol : HDL-C ratios between pitavastatin and atorvastatin [23] or simvastatin [25, 26]. However, compared with pravastatin, pitavastatin significantly ($p < 0.001$) reduced non-HDL-C levels and non-HDL-C : HDL-C and total cholesterol : HDL-C ratios across all dosages [27, 30]. Pitavastatin also significantly ($p < 0.001$) reduced apolipoprotein (apo) B levels, but did not significantly increase apoA1 levels, compared with pravastatin across all dosages [27, 30]. Reductions in apoB levels and increases in apoA1 levels did not significantly differ between the pitavastatin and atorvastatin [23] or simvastatin [25, 26] groups.

3.1.1 In Asian Patients

Treatment benefits (as assessed by changes in lipid levels) with short-term (8–16 weeks) pitavastatin 2 mg/day have also been seen in Asian patients (aged ≥20 years) with hypercholesterolemia participating in five large (randomized $n > 200$), randomized, double-blind [31, 32] or nonblind [33–35], multicentre studies in which pitavastatin was compared with atorvastatin [31, 33–35], pravastatin [32] and rosuvastatin [33]. For instance, in the double-blind study in Japanese patients (per-protocol $n = 225$) [32], significant ($p < 0.05$) mean percentage reductions from baseline to week 12 in LDL-C, total cholesterol and triglyceride levels (co-primary endpoints) were seen with both pitavastatin 2 mg once daily and pravastatin 10 mg once daily. Pitavastatin provided significant mean percentage reductions in LDL-C (38 vs. 18%; $p = 0.001$) and total cholesterol (28 vs. 14%; $p < 0.001$) levels from baseline to week 12 relative to pravastatin, although it should be noted that the doses are not equipotent. Moreover, in patients with a baseline triglyceride level of ≥150 mg/dL, pitavastatin was no less effective than pravastatin in terms of the mean percentage reduction in triglyceride levels (23 vs. 20%) [noninferiority criteria not specified]. The proportion of patients achieving the target LDL-C level of <140 mg/dL was significantly greater with pitavastatin than pravastatin (75 vs. 36%; $p < 0.05$) [32]. In the double-blind study in Taiwanese patients (randomized $n = 225$) [31], significant ($p < 0.001$) mean percentage reductions from baseline to week 12 in LDL-C (primary endpoint), total cholesterol, triglyceride and apoB levels were seen with both pitavastatin 2 mg/day and atorvastatin 10 mg/day. There was no significant difference between the pitavastatin and atorvastatin groups in terms of the primary endpoint (35 vs. 38%) [31].

In the largest (FAS $n = 285$ Japanese patients) nonblind study (of 16 weeks' duration) [33], pitavastatin 2 mg/day was no less effective than atorvastatin 10 mg/day and rosuvastatin 2.5 mg/day and rosuvastatin was no less effective than atorvastatin, as the lower limit of the 95% CI for the between-group difference in the percentage change in LDL-C levels (primary endpoint) was greater than −5%.

3.2 Longer-Term Therapy

Following completion of the phase III studies [23–27], patients could enter one of four longer-term, multicentre [36] or multinational [24, 37, 38], extension studies [two of which used a double-blind, double-dummy design ($n = 212$ [24] and 177 [37]) and two of which used a nonblind design ($n = 1202$ [38] and 537 [36])].

In the 44-week, double-blind, extension studies, patients originally randomized to receive pitavastatin 4 mg once daily ($n = 141$ [24] and 120 [37]) or an active comparator [atorvastatin 20 mg ($n = 71$) [24] or simvastatin 40 mg ($n = 57$) [37] once daily] continued to receive the same regimen, apart from those active comparator recipients who failed to meet the NCEP LDL-C target by week 8 of the core study. They had their dose uptitrated [to atorvastatin 40 mg ($n = 7$) [24] or simvastatin 80 mg ($n = 5$) [37] once daily] at the start of the extension study. In the nonblind extension studies, patients received pitavastatin 2 mg

Table 1 Short-term efficacy of pitavastatin in adults with primary hypercholesterolemia or combined (mixed) dyslipidemia. Results from six double-blind, noninferiority [23–27] or superiority [30] studies

Study	Treatment (mg od)	No. of pts	Mean change from BL to week 12 (%) [mean BL value; mg/dL]				Pts achieving target LDL-C levels (%)	
			LDL-C[a,b]	TC[b]	HDL-C[b]	TG[b]	NCEP ATP III[c]	EAS[c]
Comparison with ATO								
Budinski et al. [23]	PIT 2	315	−38[d] [184]	−28 [264]	+4 [49]	−14 [158]	57	57
	PIT 4[e]	298	−45[d] [182]	−32 [263]	+5 [50]	−19 [157]	78	79
	ATO 10	102	−38 [180]	−28 [261]	+3 [50]	−18 [157]	66	60
	ATO 20[e]	102	−44 [182]	−33 [263]	+3 [48]	−22 [162]	71	76
Gumprecht et al. [24][f]	PIT 4	274	−41 [143]	− 28 [233]	+7 [42]	− 20 [244]	77[g]	
	ATO 20	136	−43 [146]	− 32 [236]	+8 [41]	− 27 [245]	82[g]	
Comparison with PRA								
Sponseller et al. [30]	PIT 4	161	–38**[†h] [165]	–26** [247]	+6 [50]	−16 [133]		
	PRA 40	162[i]	–26[†] [164]	–18 [248]	+5 [46]	−13 [159]		
Stender et al. [27][f]	PIT 1	207	−31**[j] [164]	−22** [253]	+1 [61]	−13** [141]	83**	60**
	PIT 2	224	−39**[j] [163]	−27** [251]	+2* [60]	−15 [137]	89	80**
	PIT 4	210	−44**[j] [164]	−31** [251]	+4* [58]	−22* [145]	91	88**
	PRA 10	103	−22 [164]	−15 [250]	0 [58]	−5 [142]	65	38
	PRA 20	96	−29 [164]	−21 [253]	−1 [60]	−11 [148]	81	51
	PRA 40	102	−34 [167]	−24 [254]	+1 [59]	−15 [139]	88	66
Comparison with SIM								
Eriksson et al. [25]	PIT 4	233	−44[d] [166]	−31 [246]	+7 [47]	−20* [164]	87	87
	SIM 40	118	−44 [167]	−31 [245]	+5 [46]	−15 [164]	86	81
Ose et al. [26]	PIT 2	307	−39*[d] [184]	−28* [268]	+6 [51]	−16 [164]	70	60*
	PIT 4[e]	319	−44[d] [184]	−32 [268]	+6 [53]	−17 [155]	80	75
	SIM 20	107	−35 [184]	−25 [268]	+6 [51]	−16 [167]	65	49
	SIM 40[e]	110	−43 [184]	−31 [267]	+7 [52]	−16 [154]	78	76

ATO atorvastatin, *ATP* Adult Treatment Plan, *BL* baseline, *EAS* European Atherosclerosis Society, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *NCEP* National Cholesterol Education Program, *od* once daily, *PIT* pitavastatin, *PRA* pravastatin, *pts* patients, *SIM* simvastatin, *TC* total cholesterol, *TG* triglycerides

* $p < 0.05$, ** $p \leq 0.001$ vs. active comparator; † $p < 0.001$ vs. baseline

[a] Primary endpoint

[b] Where required, values provided in mmol/L were converted to mg/dL by dividing by a conversion factor of 0.0259 (for LDL-C, HDL-C and TC) and 0.0113 (for TG)

[c] NCEP ATP III: LDL-C targets of <160 mg/dL (4.2 mmol/L), <130 mg/dL (3.4 mmol/L) and <100 mg/dL (2.6 mmol/L) for low-, moderate- and high-risk patients, respectively; EAS: LDL-C target of <115 mg/dL

[d] Noninferiority was established for PIT versus the active comparator as the lower limit of the 95% CI for the between-group difference in the primary endpoint was greater than −6%

[e] Pts commenced therapy at the lower dosage (PIT 2 mg od, ATO 20 mg od and SIM 20 mg od), which was uptitrated after 4 weeks

[f] Some data are from the US prescribing information [18]

[g] Data from ClinicalTrials.gov (NCT00309751)

[h] Superiority was established for PIT versus the active comparator, although the details were not reported

[i] For the LDL-C level assessment, $n = 161$

[j] Noninferiority was established for PIT versus the active comparator as the lower limit of the 95% CI for the between-group difference in the primary endpoint was greater than −6%. A subsequent analysis demonstrated that the between-group difference was statistically significant

[36] or 4 mg [38] once daily for 52 [38] or 60 [36] weeks, with the exception of 90 patients in the longer nonblind extension study who were uptitrated to pitavastatin 4 mg once daily at, or after, week 8 if the NCEP ATP III LDL-C target had not been reached [36]. In the shorter nonblind extension study, there was a gap of 2–280 days (median 104 days) between the end of the core studies and the start of the extension study (owing to delays in obtaining ethical

approval) for 1174 patients [38]. For all of the extension studies, baseline refers to baseline of the core study [24, 36–38].

Pitavastatin provided sustained improvements from baseline in LDL-C levels over a further 44–60 weeks of treatment (Table 2). Moreover, in a post hoc analysis of one study, pitavastatin 4 mg once daily was no less effective than atorvastatin 20 or 40 mg once daily at extension week 16 [adjusted mean treatment difference of 0.11% (95% CI −5.23, 5.44)] and extension week 44 (Table 2) [24]. NCEP and EAS LDL-C target attainment was generally maintained in the four extension studies (Table 2). Among the 90 patients who were uptitrated to pitavastatin 4 mg once daily in the longer nonblind extension study, 70 and 79% achieved NCEP and EAS LDL-C targets at week 60 [36].

The beneficial effects of pitavastatin on other lipid parameters observed in the core studies were maintained in the extension studies. For instance, improvements in total cholesterol, HDL-C and triglyceride levels were sustained over longer-term (44–60 weeks) treatment, with pitavastatin and atorvastatin or simvastatin improving these parameters to a generally similar extent (Table 2). Of note, lipid profiles among the 90 patients who were uptitrated to pitavastatin 4 mg once daily at the start of the longer nonblind extension study were broadly similar to those of the entire efficacy population [36].

3.2.1 *In Asian Patients*

Treatment benefits were sustained in Asian patients participating in longer-term (up to 60 months) studies [22, 39–42]. For example, in LIVES ($n = 18{,}031$ Japanese patients), significant ($p < 0.001$) mean percentage reductions in LDL-C levels relative to baseline (29%) were seen following 24 months' therapy with pitavastatin 1–4 mg/day (<1% of patients received the 4 mg/day dosage) [22]. A treatment effect was observed as early as week 4, with pitavastatin therapy associated with a significant ($p < 0.001$) reduction in LDL-C levels at this timepoint. The effect of pitavastatin on LDL-C levels was seen in patients with or without a history of previous statin therapy, in those with or without concomitant hepatic or renal impairment and in those with or without diabetes mellitus [22].

The proportions of patients in the low-risk, intermediate-risk, high-risk and secondary prevention categories ($n = 796$, 7729, 4713 and 1107) achieving Japan Atherosclerosis Society (JAS) target LDL-C levels (of <160, <140, <120 and <100 mg/dL, respectively) were 88, 83, 67 and 50% [22]. Moreover, switching from a previous medication to pitavastatin was associated with an increase in the proportion of patients in the low-risk (from 68 to 86%), intermediate-risk (from 36 to 84%), high-risk

Table 2 Longer-term efficacy of pitavastatin in adults with primary hypercholesterolemia or combined (mixed) dyslipidemia. Results from four multicentre [36] or multinational [24, 37, 38] extension studies

Study	Treatment (mg od)	No. of pts	Mean change from BL[a] to study end[b] (%) [mean BL value; mg/dL]				Pts achieving target LDL-C levels (%)	
			LDL-C[c]	TC[c]	HDL-C[c]	TG[c]	NCEP ATP III	EAS
Eriksson et al. [37]	PIT 4	120	−42 [165]	−27 [244]	+14 [47]	−12 [165]	82[d]	84
	SIM 40 or 80	57	−41 [169]	−27 [250]	+15 [46]	−12 [176]	75	74
Gumprecht et al. [24]	PIT 4	141[e]	−41[f] [144]	−28 [235]	+13 [43]	−22 [246]	≈80[g]	>85[g]
	ATO 20 or 40	71	−41[f] [146]	−29 [236]	+17 [41]	−26 [248]	≈80[g]	>85[g]
Ose et al. [38]	PIT 4	1202[e]	−43 [183]	−30 [266]	+14 [51]	−17 [160]	74	74
Stender et al. [36]	PIT 2 or 4	537	−43[h] [164[g]]	−29 [252]	+10 [59]	−20 [144]	94	89

ATO atorvastatin, *ATP* Adult Treatment Plan, *BL* baseline, *EAS* European Atherosclerosis Society, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *NCEP* National Cholesterol Education Program, *od* once daily, *PIT* pitavastatin, *pts* patients, *SIM* simvastatin, *TC* total cholesterol, *TG* triglycerides

[a] Of the core studies

[b] Week 44 [24, 37], week 52 [38] or week 60 [36]

[c] Where required, values provided in mmol/L were converted to mg/dL by dividing by a conversion factor of 0.0259 (for LDL-C, HDL-C and TC) and 0.0113 (for TG)

[d] NCEP ATP III and EAS targets were achieved by 86 and 79% of PIT recipients and 88 and 90% of SIM recipients at week 16

[e] For mean baseline values, $n = 143$ [24] and 1346 [38]

[f] Noninferiority (in a post hoc analysis) was established for PIT versus the active comparator as the lower limit of the 95% CI for the between-group difference in this endpoint was greater than −6% [adjusted mean treatment difference of −0.02% (95% CI −5.46, 5.41)]

[g] Value estimated from a graph

[h] Approximate value

(from 25 to 64%) and secondary prevention (from 21 to 49%) categories who achieved JAS target LDL-C levels. Across the categories, reductions from baseline in JAS target LDL-C levels of 20, 30 and 40% were seen in 76–80, 60–64 and 39–42% of patients [22].

Relative to baseline, pitavastatin provided significant ($p < 0.001$) mean percentage reductions in triglyceride levels (6%), including in patients with a baseline triglyceride level of >150 mg/dL (23%), and significant ($p < 0.001$) mean percentage improvements in HDL-C levels (4%), including in patients with a baseline HDL-C level of <40 mg/dL (20%) [22].

In the 36-month extension ($n = 6582$) [41] of LIVES, the mean reduction in LDL-C levels was sustained relative to baseline (of LIVES) [31%; $p < 0.001$]. This was seen irrespective of whether patients had a history of ischemic heart disease. Total cholesterol (mean change of 22%) and triglyceride (mean change 7%) levels were also significantly ($p < 0.001$) reduced at month 60 relative to baseline and HDL-C levels were significantly ($p < 0.001$) improved (mean change 6%), including in patients with a baseline HDL-C level of <40 mg/dL (mean change 29%) [41].

4 Tolerability of Pitavastatin

Oral pitavastatin 1–4 mg once daily was generally well tolerated in adults participating in the short-term (8–16 weeks) studies [23–27, 30–35] discussed in Sect. 3. The tolerability profile of pitavastatin was generally similar to those of atorvastatin [23, 24], pravastatin [27, 30] and simvastatin [25, 26]. The nature and incidence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) in pitavastatin recipients were generally similar to those in active comparator recipients, with most being mild or moderate in severity and considered to be unrelated to the study medication. There were few serious TEAEs (≤2% of patients) and treatment discontinuations (1–5%) reported in each of the pitavastatin groups, with the incidences of each generally similar between the pitavastatin and active comparator groups [23–27, 30]. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels >3 × the upper limit of normal (ULN) and elevations in creatine kinase (CK) levels >5 × ULN were uncommon [24–27, 30]. Myopathy and rhabdomyolysis were not reported [26, 27, 30].

Longer-term (44–60 weeks) pitavastatin 2 or 4 mg once daily was also generally well tolerated in extension studies, with no new adverse events reported [22, 24, 36–38, 40]. The nature and incidence of TEAEs were generally similar across the extension studies, with most being mild or moderate in severity [24, 36–38]. In the shorter nonblind extension study, increased blood creatinine kinase levels (6% of patients), nasopharyngitis (5%) and myalgia (4%) were the most frequently reported TEAEs [38]. There were no cases of myopathy, rhabdomyolysis or severe myalgia [36, 38]. Overall, 2–7% of pitavastatin recipients [24, 36–38], 1% of atorvastatin recipients [24] and 11% of simvastatin recipients [37] discontinued therapy. Where reported, fewer than 1% of patients died, with none of the deaths considered to be related to the study medication [36, 38]. Clinically relevant increases in ALT, AST and CK levels were uncommon with long-term pitavastatin therapy [24, 36–38].

In the studies in Asian patients discussed in Sects. 3.1.1 and 3.2.1, the tolerability profile of pitavastatin 2 mg/day was generally similar to those seen with atorvastatin [31, 33–35], pravastatin [32] and rosuvastatin [33]. Moreover, the tolerability profile of pitavastatin 1–4 mg/day in Japanese patients in LIVES [22], a 24-month prospective post-marketing surveillance study, was consistent with those seen in the longer-term extension studies [24, 36–38]. Adverse reactions (i.e. adverse events whose causal relationship to the study medication could not be ruled out) occurred in 10% of 19,925 patients and were mostly mild in severity [22]. Major adverse reactions (each occurring in 1–3% of patients) were laboratory abnormalities [elevations in serum ALT, AST, CK and γ-glutamyltransferase (GGT) levels] and myopathy-associated symptoms (myalgia). Serious adverse reactions (the most frequent being abnormal hepatic function, liver disorder and cataract operation) occurred in fewer than 1% of patients. During the study, 7% of patients discontinued treatment because of adverse events. Hepatopathy-associated adverse reactions (elevations in ALT, AST and γ-GGT levels, etc.), most of which were mild in severity, occurred in 3% of patients. Myopathy-associated adverse reactions (elevations in CK levels, myalgia, etc.), most of which were mild in severity, occurred in 5% of patients. One case of rhabdomyolysis was diagnosed [22].

4.1 Effects on Glucose Metabolism and Diabetes Risk

There is evidence to suggest that statins as a class increase blood glucose levels, and that in patients at a high risk of developing diabetes they may induce a level of hyperglycemia that requires therapeutic intervention [6]. The effect of pitavastatin on glucose metabolism parameters has been assessed in several studies, including those discussed in Sect. 3, the J-PREDICT study (a 60-month, prospective, nonblind, multicentre Japanese study that assessed the effect of pitavastatin on the incidence of diabetes in 1269 patients with IGT; data available as abstracts) [43–48] and two meta-analyses [4, 49].

In short- and longer-term studies in non-Asian patients discussed in Sects. 3.1 and 3.2, pitavastatin did not appear to adversely affect glucose metabolism parameters [e.g. fasting blood glucose (FBG), fasting plasma glucose (FPG), fasting plasma insulin, HbA_{1c}, HOMA-IR] [24, 25, 27, 30]. For instance, in the noninferiority study in patients with concomitant type 2 diabetes [24], therapy with pitavastatin was associated with a non-significant mean change from baseline in FBG levels at both week 12 (of the core study) and week 44 (of the extension study) [+2 and +4%]. In contrast, atorvastatin was associated with a significant ($p < 0.05$) mean change from baseline in FBG levels at these timepoints (+7 and +7%). Of note, a post hoc analysis determined that the between-group difference at week 12 was significant ($p = 0.0054$) [24]. Moreover, there were no changes from baseline to week 12 in mean plasma glucose levels following therapy with pitavastatin or simvastatin in the noninferiority study in patients with ≥2 cardiovascular risk factors [25] and no clinically relevant changes in terms of glucose metabolism parameters [e.g. FPG, fasting plasma insulin, HbA_{1c}] in either the pitavastatin or pravastatin groups in the superiority study [30].

In J-PREDICT, subjects with IGT according to World Health Organization criteria were randomized to receive pitavastatin 1 or 2 mg/day in combination with lifestyle modification advice or lifestyle modification advice alone for 60 months [50, 51]. The primary endpoint of J-PREDICT was the cumulative incidence of diabetes (defined as at least one FPG level ≥126 mg/dL or 2-h plasma glucose level ≥200 mg/dL) as assessed by a 75 g oral glucose tolerance test every 6 months. Eligible patients were aged 30–74 years, had LDL-C levels of 100–159 mg/dL or total cholesterol levels of 180–239 mg/dL, FPG levels of 100–125 mg/dL, HbA_{1c} of 5.9–6.4%, body mass index (BMI) ≥24 kg/m^2 and/or a second-degree relative with diabetes [50, 51].

Pitavastatin plus lifestyle modification advice was associated with a lower incidence of diabetes [40% (213/534) and 46% (254/556) of patients; 163 vs. 186 cases per 1000 person-years], corresponding to an 18% reduction in the risk of progression from IGT to diabetes relative to lifestyle modification advice alone [hazard ratio (HR) 0.82 (95% CI 0.68, 0.99); $p = 0.041$] [45–47]. Subgroup analyses suggested that the addition of pitavastatin to lifestyle modification advice did not increase the incidence of diabetes compared with lifestyle modification advice alone across various patient subgroups [45, 47]. In fact, the risk of progression from IGT to diabetes with pitavastatin plus lifestyle modification advice compared with lifestyle modification advice alone was significantly reduced (by 35%) in patients without hypertension [HR 0.65 (95% CI 0.50, 0.84); $p = 0.01$], but not in patients with hypertension [HR 1.08 (95% CI 0.82, 1.42)], with a p value for interaction of 0.01 [44]. Moreover, pitavastatin plus lifestyle modification advice significantly reduced the risk of progression from IGT to diabetes compared with lifestyle modification advice alone in women [HR 0.68 (95% CI 0.49, 0.93); $p = 0.02$], but not in men [HR 0.97 (95% CI 0.78, 1.21)] (p value for interaction not reported) [48]. The treatment effect of pitavastatin plus lifestyle modification advice in women was not associated with age (<55 years, 54–64 years, ≥65 years) [48]. The incidence of diabetes increased alongside the increase in BMI in both the pitavastatin plus lifestyle modification advice (from 121 to 181 per 1000 person-years) and lifestyle modification advice only (from 170 to 209 per 1000 person-years) groups, with a significant reduction in the risk of progression from IGT to diabetes with pitavastatin plus lifestyle modification advice relative to lifestyle modification advice alone observed only in patients with a BMI of <23.4 kg/m^2 [HR 0.61 (95% CI 0.42, 0.89); $p = 0.0096$] [43].

Neutral effects on glucose metabolism parameters (e.g. FPG, HbA_{1c}, HOMA-IR, insulin) with short-term (12 weeks) pitavastatin 2 mg/day therapy have been observed in Japanese patients with hyperlipidemia and diabetes in a subgroup analysis [52] of a multicentre study [35] and in a retrospective study [53]. Moreover, glucose metabolism parameters (e.g. blood glucose, HbA_{1c}) did not appear to be adversely affected following 24 months' therapy with pitavastatin in Asian patients participating in LIVES [22, 54].

Generally neutral effects on glucose homeostasis parameters (e.g. HbA_{1c}, HOMA-IR, serum insulin) have also been observed in adults with metabolic syndrome [55], although owing to the small number of patients ($n = 12$) further data would be of interest.

Results from a meta-analysis ($n = 3236$ and 1579 in the pitavastatin and control groups) [49] of 15 studies in patients without diabetes were consistent with those from prospective clinical studies, with pitavastatin demonstrating a neutral effect on glucose metabolism and the development of diabetes. Specifically, the effects of pitavastatin on FBG levels [mean difference −0.01 mg/dL (95% CI−0.77, +0.74)] and HbA_{1c} (mean difference −0.03% [95% CI −0.11, +0.05]) did not significantly differ from those of the control (placebo or other statin). Moreover, although it was not significant, pitavastatin was associated with a 30% reduction in the risk of new-onset diabetes [relative risk 0.70 (95% CI 0.30–1.61)]. Of note, according to predefined subgroup analyses, there were no dose-dependent (pitavastatin 2 or 4 mg/day) or follow-up time (12 or >12 weeks) effects on FBG levels, HbA_{1c} and the incidence of new-onset diabetes [49]. In a recent network meta-analysis of 27 studies, pitavastatin ranked last out of the eight drug regimens assessed in increasing the risk of

developing diabetes [4]. Specifically, compared with placebo, atorvastatin 80 mg [odds ratio (OR) 1.34 (95% CI 1.14–1.57)] and rosuvastatin [OR 1.17 (95% CI 1.02–1.35)] were ranked first and second and significantly increased the risk of developing diabetes. Simvastatin 80 mg [OR 1.21 (95% CI 0.99–1.49)] was ranked third, followed by lower dose simvastatin [OR 1.13 (95% CI 0.99–1.29)], lower dose atorvastatin [OR 1.13 (95% CI 0.94–1.34)], pravastatin [OR 1.04 (95% CI 0.93–1.16)], lovastatin [OR 0.98 (95% CI 0.69–1.38)] and then pitavastatin [OR 0.74 (95% CI 0.31–1.77)] [4].

5 Dosage and Administration of Pitavastatin

Oral pitavastatin is approved in various EU countries under the Decentralized Procedure, with the UK as the Reference Member State [56], for the reduction of elevated total cholesterol and LDL-C levels in adults with primary hypercholesterolemia, including heterozygous familial hypercholesterolemia, and combined (mixed) dyslipidemia, when response to diet and other non-pharmacological measures is inadequate [6].

The usual starting dosage is 1 mg once daily, with dose adjustments made at ≥4-week intervals to a maximum recommended dosage of 4 mg once daily [6]. Dosages should be individualized according to LDL-C levels, the goal of therapy and patient response. Pitavastatin may be administered with or without food (Sect. 2.2); patients should be on a cholesterol-lowering diet before and during treatment [6].

Pitavastatin is contraindicated in patients with severe hepatic impairment, active liver disease or unexplained persistent elevations in serum transaminase levels (>3 × ULN); in those with myopathy; in those receiving concomitant cyclosporine; and in those who are pregnant or breast-feeding [6]. The 4 mg once daily dosage is not recommended in patients with severe renal impairment or those with mild to moderate hepatic impairment (Sect. 2.2). Therapy should not be started in patients with CK levels >5 × ULN [6].

Local prescribing information should be consulted for detailed information, including other contraindications, potential drug interactions, use in special patient populations, and warnings and precautions.

6 Place of Pitavastatin in the Management of Hypercholesterolemia

Dyslipidemia is one of the major risk factors for the development of CVD, with current European guidelines recommending LDL-C levels as the primary lipoprotein target for reducing CVD risk [1, 2]. There is unequivocal evidence that reducing plasma LDL-C levels will reduce CVD risk [2] and the intensity of preventative actions should be tailored to the patient's total CVD risk [1]. Treatment recommendations include monotherapy or combination therapy with statins, bile acid-binding protein modulators, cholesterol absorption inhibitors (e.g. ezetimibe), fibrates, niacin and/or PCSK9 protein modulators [1, 2]. Statins are generally chosen as first-line therapy and have clearly demonstrated their efficacy in reducing CVD morbidity and mortality [1, 2]. Of note, reductions in LDL-C levels vary between individuals, between doses and between statins, with atorvastatin, rosuvastatin and pitavastatin the more potent statins [1].

The short- and longer-term lipid-lowering efficacy of pitavastatin has been demonstrated in adults with uncontrolled primary hypercholesterolemia or combined (mixed) dyslipidemia (Sect. 3). Pitavastatin was generally noninferior to presumed equipotent dosages of atorvastatin and simvastatin (including in patients with ≥2 cardiovascular risk factors) and more effective than pravastatin in terms of the mean percentage change from baseline in LDL-C levels (Sect. 3.1). NCEP ATP III and EAS target LDL-C levels were achieved by over half of the patients receiving pitavastatin or an active comparator in clinical studies. Beneficial effects with short-term pitavastatin therapy on other lipid parameters, including total cholesterol, HDL-C and triglyceride levels, were also seen in these studies (Sect. 3.1). In four longer-term extension studies, the efficacy of pitavastatin was sustained during treatment for up to 60 weeks (Sect. 3.2). Such treatment benefits are consistent with those observed in short-term (8–16 weeks) comparisons with atorvastatin, pravastatin and rosuvastatin (Sect. 3.1.1) and in longer-term (up to 60 months) studies (Sect. 3.2.1) in Asian patients. It is worth noting that patients who achieved JAS LDL-C [HR 0.43 (95% CI 0.32–0.590)] or HDL-C [HR 0.41 (95% CI 0.28–0.62)] targets with pitavastatin in the LIVES extension study had a significantly ($p < 0.0001$) lower incidence of total cardiovascular events (i.e. cardiovascular events, cerebrovascular events and sudden death) than those who did not [41]. However, the lipid-lowering effects of pitavastatin on cardiovascular morbidity and mortality have yet to be determined [6, 18].

Pitavastatin was generally well tolerated in adults participating in short-term (8–16 weeks) studies, with its tolerability profile remaining consistent over longer-term (up to 24 months) therapy (Sect. 4). The short-term (12 weeks) tolerability profile of pitavastatin was generally similar to those of atorvastatin, pravastatin and simvastatin.

Diabetes is an independent risk factor for CVD [1]. Moreover, there is evidence to suggest that statins, as a class, increase the risk of dysglycemia and the development of type

2 diabetes [1] and this is clearly identified in prescribing information, although this risk is outweighed by the beneficial effects of statins on CVD [57]. At present, no firm conclusions can be reached about whether or not specific statins (or dosage regimens) are associated with a higher risk of new-onset diabetes [58]. Indeed, a recent meta-analysis ($n = 103{,}261$) of 18 studies in patients with CVD found that statins significantly increased the likelihood of developing diabetes by 12% [OR 1.12 (95% CI 1.05–1.21; $p = 0.002$)] [4]. Age >70 years, female sex, Asian ethnicity and risk factors for type 2 diabetes (e.g. components of the metabolic syndrome) appear to be most frequently associated with the development of new-onset diabetes during statin therapy [10]. Abnormalities in the plasma lipidome associated with type 2 diabetes appear to precede the onset of type 2 diabetes, being present in patients with prediabetes [59]. Of interest, there is evidence that treatment with pitavastatin attenuates the plasma lipidome in adults with mixed dyslipidemia and metabolic syndrome (Sect. 2.1). Further investigation to identify the subgroups of patients requiring treatment with statins who are at greatest risk of new-onset diabetes would be of interest [58].

The mechanism by which statins affect glucose homeostasis is not yet completely understood; however, it is thought to be related to reduced HMG-CoA reductase activity (the target of statin therapy), increased insulin resistance and/or impaired β-cell function (Sect. 2.1). For instance, there is an inverse relationship between adiponectin levels and visceral obesity and insulin resistance, with high adiponectin levels associated with a substantially reduced risk of type 2 diabetes [10]. Of note, pitavastatin has demonstrated an increase in adiponectin levels (Sect. 2.1).

Although the risk of dysglycemia and the development of type 2 diabetes appears to be a class effect among statins, and this is mentioned in special warnings and precautions in prescribing information, individual variation has been observed, with atorvastatin, fluvastatin, rosuvastatin and simvastatin generally appearing to adversely affect glucose metabolism parameters, and pitavastatin and pravastatin appearing to have neutral effects [10]. Indeed, in a recent network meta-analysis of 27 studies, pitavastatin ranked last out of the eight drug regimens assessed in increasing the risk of developing diabetes, with atorvastatin 80 mg and rosuvastatin ranked first and second (Sect. 4.1). Moreover, it did not appear to adversely affect glucose metabolism parameters in short- and longer-term prospective and post-marketing surveillance studies in adults and, in combination with lifestyle modification advice, was associated with a lower incidence of diabetes, corresponding to an 18% reduction in the risk of progression from IGT to diabetes relative to lifestyle modification advice alone in J-PREDICT (a longer-term study in Japanese subjects with IGT) [Sect. 4.1]. The fully published data are awaited with interest. Based on data from the prospective and post-marketing surveillance studies of pitavastatin, and in contrast to the UK summary of product characteristics (SPC) for the other available statins [60–64], the pitavastatin UK SPC indicates that there has been no confirmed signal of a diabetes risk for pitavastatin [6].

In conclusion, pitavastatin demonstrated lipid-lowering efficacy and was generally well tolerated over the short- and longer-term in adults with uncontrolled primary hypercholesterolemia or combined (mixed) dyslipidemia, including those aged ≥65 years and those with type 2 diabetes or ≥2 cardiovascular risk factors. It was generally no less effective than other statins, including atorvastatin, pravastatin and simvastatin and does not appear to adversely affect glucose metabolism parameters or the risk of developing diabetes. Thus, pitavastatin continues to be an effective and well tolerated first-line treatment option in patients with primary hypercholesterolemia and combined (mixed) dyslipidemia, including those at risk of developing type 2 diabetes.

Data Selection Pitavastatin: 167 records identified	
Duplicates removed	28
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	2
Excluded during initial selection (e.g. preclinical study; review; case report; not randomized trial)	31
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	42
Cited efficacy/tolerability articles	25
Cited articles not efficacy/tolerability	39
Search Strategy: EMBASE, MEDLINE and PubMed from 2012 to present. Previous Adis Drug Evaluation published in 2012 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Pitavastatin, Livalo, Livazo, Alipza, Vezepra, Redevant, Trolise, Itavastatin, NK-104, Nisvastatin, P-872441, hypercholesterolaemia. Records were limited to those in English language. Searches last updated 17 January 2017	

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Compliance with Ethical Standards

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