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Liraglutide: A Newly Approved Incretin Mimetic

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The prevalence of type II diabetes mellitus (DM) and obesity continue to increase in the United States. According to National Health and Nutrition Examination Survey (NHANES) data, the prevalence of obesity in adults has increased from 15% in 1980 to nearly 34% in 2008.[1] DM is associated with obesity, as almost 90% of patients newly diagnosed with type II DM are overweight.[2] Many patients are uncontrolled on current available medications, and often have an increase in weight or hypoglycemia due to therapy. There remains a need for new treatment options in DM that control glucose levels without causing the usual side effects.[3]

The Food and Drug Administration approved liraglutide, an incretin mimetic, on January 25, 2010. Novo Nordisk manufactures liraglutide and markets it under the brand name Victoza®. Liraglutide is approved for use in adults with type II DM in combination with diet and exercise to improve glycemic control.[4] The objective of this article is to review liraglutide with a focus on both efficacy and safety.

Pharmacology

The incretins are insulinotropic hormones released by the gastrointestinal tract in response to increased glucose levels after meals. The two major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[3] Liraglutide acts as a GLP-1 receptor agonist, which places it in the same class of medications as Byetta® (exenatide). GLP-1 receptor agonists stimulate glucose-dependant insulin release from pancreatic beta-cells, promote beta-cell proliferation, decrease postprandial glucagon secretion, delay gastric emptying, and increase satiety.[5]

Pharmacokinetics

After subcutaneous administration, plasma concentrations reached their peak in 8-12 hours (**Table 1**). Liraglutide has a long elimination half-life of 13 hours.[4,6] This extended half-life is a function of liraglutide's resistance to dipeptidyl peptidase IV (DPP-IV), which is responsible for GLP-1 metabolism. The resistance to DPP-IV and other peptidases allows for once daily dosing.[6] Intact liraglutide is not found in urine or feces, and only a small percentage of related metabolites were recovered in each.

Special Populations

Approximately 20% of the patients enrolled in phase III clinical trials were considered elderly (>65 years old). These trials found no changes in safety or efficacy, so no dosage adjustment is necessary in the elderly. Pediatric patients have not been included in

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Table 1. Pharmacokinetics of Liraglutide.

PROPERTY	LIRAGLUTIDE
Peak Concentrations	8-12h
V_d	~13L
$T_{1/2}$	13h
Plasma Protein Binding	≥ 98%
Absolute bioavailability	55%
Excretion	Urine (6%) and Feces (5%)

$T_{1/2}$ = elimination half-life; V_d = volume of distribution

studies, and recommended use is in adults only. Race and gender also had minimal effects on liraglutide pharmacokinetics. Body weight does alter the pharmacokinetic profile of liraglutide. As body weight increases, the exposure to drug decreases. However, no clinically significant change in exposure or outcomes was associated with patients weighing less than 160 kg. Liraglutide does not require a dosage adjustment based on weight, but patients weighing over 160 kg were not included in any studies. Patients with varying degrees of hepatic and renal disease were included in clinical trials. While these patients had a slightly lower AUC, it did not correlate to worse outcomes clinically. Caution is advised, but no dosage adjustments are recommended.[4]

Drug Interactions

Liraglutide may decrease the absorption of some oral medications by delaying gastric emptying. Clinical trials failed to show a clinically relevant change in the absorption of oral medications, but use caution with oral medications in combination with liraglutide. *In vitro* studies showed limited potential for relevant interactions involving CYP enzymes and plasma protein binding.[4]

CLINICAL TRIALS

The Liraglutide Effect and Action in Diabetes (LEAD) trial series established both the clinical safety and efficacy of liraglutide. The LEAD series consisted of six phase III trials that investigated over 4,400 patients with DM. These trials compared liraglutide to rosiglitazone, insulin glargine, glimepiride, and exenatide. The two most decisive trials were liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono) and liraglutide once a day versus exenatide twice a day for type 2 diabetes (LEAD-6). LEAD-3 Mono proved safety and efficacy as a monotherapy, while LEAD-6 was a favorable direct comparison with exenatide. The rest of the LEAD trials studied liraglutide as part of various combination therapies (**Table 2**). Liraglutide was not studied in patients less than 18 years old or in combination with insulin during phase III clinical trials.[3,4]

LEAD-3 Mono was conducted as a 52 week, multicenter, double-blind, randomized controlled trial that included 746 early DM patients. The inclusion criteria was 18-80 years, a body mass index (BMI) ≤ 45 kg/m^2, and a previous diagnosis of DM. The study excluded participants if they used insulin within the last 3 months, had a history of severe hypoglycemia, or had impaired liver function. Groups were randomly assigned (1:1:1) to receive subcutaneous liraglutide 1.2 mg daily, subcutaneous liraglutide 1.8 mg daily, or oral glimepiride 8 mg daily. The primary endpoint was a change in hemoglobin A_{1c} from baseline after 52 weeks of treatment. Six patients treated with liraglutide discontinued treatment due to vomiting and no patients were lost from the glimepiride group. Both liraglutide treatment groups showed a significantly greater decrease in A_{1c} than the glimepiride treatment group. The decrease in the glimepiride group was 0.51%, in comparison to the liraglutide 1.2 mg 0.84% decrease (-0.33% difference, p=0.0014) and to liraglutide 1.8 mg 1.14% decrease (-0.62 difference, p<0.0001). Liraglutide patients overall showed weight loss of 2.3 kg, while the glimepiride group increased 1.1 kg in weight. The glimepiride treatment also led to more hypoglycemia. The authors concluded that liraglutide is safe and effective as initial monotherapy in DM treatment, and produces greater reductions in A_{1c}, weight, and hypoglycemia than glimepiride.[7]

LEAD-6 compared GLP-1 receptor agonists liraglutide and exenatide. This trial had a 26 week randomized, open-label, multicenter, parallel group design. Participants had to be aged 18-80 years, have DM with an A_{1c} between 7-11%, have a BMI ≤ 45 kg/m^2, and being treated with maximal doses of metformin, a sulfonylurea, or both for at least 3 months. Patients were excluded if previously treated with insulin, had cancer, uncontrolled hypertension, impaired liver function, or cardiovascular disease. The study randomly assigned (1:1) all 464 participants to receive either subcutaneous liraglutide 1.8 mg daily or subcutaneous exenatide 10 µg twice daily. The primary endpoint was change in A_{1c} from baseline following 26 weeks of treatment. The average decrease in A_{1c} from baseline was significantly greater in the liraglutide treated group than in the exenatide treated group (-1.12% vs. -0.79%, p<0.0001). Both drugs caused a comparable reduction in weight, and patients generally tolerated both well, but there was slightly less persistent nausea and minor hypoglycemia with liraglutide. The authors concluded that

Table 2. Summary of Clinical Trials of Liraglutide.[6,-8, 11-14]

Trial	Design	Treatment	Results	
			Primary Endpoints	Secondary Endpoints
Elbrond B, et al. (2002)	DB, R, PC Dose escalation in healthy males n = 72	liraglutide 1.25, 2.5, 5.0, 10.0, 12.5, 15.0, 17.5, and 20.0 µg/kg Placebo	$T_{1/2}$ = 11-15 hours Absolute bioavailability = 55% Zero serious ADR's	Increase in insulin secretion of 2.74 mU/l [1.75–4.28] (p = 0.0002)
Visboll T, et al. (2007)	DB, R, PC Safety and efficacy in type 2 DM x 14 weeks n = 163	liraglutide 1.90, 1.25, or 0.65 mg Placebo	Change in A_{1c}: 1.90 mg: -1.74% [a] 1.25 mg: -1.69% [a] 0.65 mg: -1.27% [a]	NR
Marre M, et al. (2009) LEAD-1 SU	DB, R, PC, MC Phase III trial liraglutide or rosiglitazone added to glimepiride 26 weeks n = 1,041	liraglutide (0.6, 1.2, 1.8 mg/day) or rosiglitazone 4 mg/day with glimepiride (2–4 mg/day)	Change in A_{1c}: liraglutide 0.6 mg: -0.6% [a] liraglutide 1.2 mg: -1.1% [a] liraglutide 1.8 mg: -1.1% [a] rosiglitazone 4 mg: -0.4% [a] placebo: +0.2%	Change in body weight: liraglutide 0.6 mg: +0.7kg [b] liraglutide 1.2 mg: +0.3 kg [b] liraglutide 1.8 mg: -0.2 kg [b] rosiglitazone 4 mg: +2.1kg placebo: -0.1 kg
Nauck M, et al. (2009) LEAD-2 Met	DB, R, PC, MC Phase III trial liraglutide or glimepiride added to metformin 26 weeks n = 1,091	liraglutide (0.6, 1.2, 1.8 mg/day) or glimepiride 4 mg/day with metformin 1 g twice daily	Change in A_{1c}: liraglutide 0.6 mg: -0.7% [a] liraglutide 1.2 mg: -1.0% [a] liraglutide 1.8 mg: -1.0% [a] glimepiride 4 mg: -1.0% [a] placebo: +0.1%	Change in body weight: liraglutide 0.6 mg: -1.8kg [b] liraglutide 1.2 mg: -2.6 kg [b] liraglutide 1.8 mg: -2.8 kg [b] glimepiride 4 mg: +1.0kg placebo: -1.5 kg
Garber A, et al. (2009) LEAD-3 Mono	DB, R, C, MC Phase III trial monotherapy liraglutide vs. glimepiride 52 weeks n = 746	liraglutide 1.2 mg/day liraglutide 1.8 mg/day glimepiride 8 mg/day	Change in A_{1c}: liraglutide 1.2 mg: -0.8% [c] liraglutide 1.8 mg: -1.1% [b] glimepiride 4 mg: -0.5%	Change in body weight: liraglutide 1.2 mg: -2.1 kg [b] liraglutide 1.8 mg: -2.5 kg [b] glimepiride 4 mg: +1.1 kg
Zinman B, et al. (2009) LEAD-4 Met + TZD	DB, R, PC, MC Phase III trial liraglutide + metformin and rosiglitazone 26 weeks n = 533	liraglutide 1.2 mg/day liraglutide 1.8 mg/day with metformin 1 g twice daily and rosiglitazone 4 mg twice daily	Change in A_{1c}: liraglutide 1.2 mg: -1.5% [a] liraglutide 1.8 mg: -1.5% [a] placebo: -0.5%	Change in body weight: liraglutide 1.2 mg: -1.0 kg [a] liraglutide 1.8 mg: -2.0 kg [a] placebo: +0.6 kg
Russell D, et al. (2009) LEAD-5 Met +SU	DB, R, PC, MC Phase III trial liraglutide vs. insulin glargine 26 weeks n = 581	liraglutide 1.8 mg/day or insulin glargine with metformin 1 g twice daily and glimepiride 4 mg/day	Change in A_{1c}: liraglutide 1.8 mg: -1.3% [a] insulin glargine: -1.1% [a] placebo: -0.2%	Change in body weight: liraglutide 1.8 mg: -1.8 kg [b] insulin glargine: +1.6 kg placebo: -0.4 kg
Buse J, et al. (2009) LEAD-6	OL, R, C, MC Phase III trial liraglutide vs. exenatide 26 weeks n = 464	liraglutide 1.8 mg/day or exenatide 10 µg twice daily with optimized SU, Met, or both	Change in A_{1c}: liraglutide 1.8 mg: -1.1% [b] exenatide 10 µg: -0.8%	Change in body weight: liraglutide 1.8 mg: -3.2 kg exenatide 10 µg: -2.9 kg

A_{1c} = hemoglobin A_{1c}; **ADR** = adverse drug reactions; **DB** = double-blind; **LEAD** = Liraglutide Effect and Action in Diabetes; **MC** = multicenter; **Met** = metformin; **Mono** = monotherapy; **NR** = none reported; **OL** = open-label; **PC** = placebo-controlled; **R** = randomized; **SU** = sulfonylurea; **$T_{1/2}$** = elimination half-life; **TZD** = Thiazolidinedione.

[a] p<0.0001 versus placebo

[b] p<0.0001 versus comparator

[c] p<0.0014 versus comparator

Table 3. Adverse Events of Selected Diabetic Therapies During Clinical Trials.[7,8,10]

Adverse Event	Liraglutide[a] (n=497)	Glimepiride[a] (n=248)	Liraglutide + Metformin[b] (n=724)	Glimepiride + Metformin[b] (n=242)	Placebo + Metformin[b] (n=121)	Liraglutide[c] (n=235)	Exenatide[c] (n=232)
Nausea	**28.4**	8.5	**15.2**	3.3	4.1	25.5	28
Diarrhea	**17.1**	8.9	**10.9**	3.7	4.1	12.3	12.1
Vomiting	**10.9**	3.6	**6.5**	0.4	0.8	6.0	9.9
Constipation	9.9	4.8	NR	NR	NR	12.0	6.0
Headache	9.1	9.3	9.0	9.5	6.6	8.9	10.3
Hypoglycemia	**9.7**	25	3.6	**22.3**	2.5	**25.5**	33.6

Data expressed as percentages. Bolded terms reported as significantly different from comparator or placebo.
NR = Not Recorded.
[a] LEAD-3
[b] LEAD-2
[c] LEAD-6

when weight loss and hypoglycemia are concerns, liraglutide might be a treatment option for type II DM.[8]

Safety

Liraglutide carries a black box warning for an increased risk of thyroid C-cell tumors. The FDA assigned this warning due to two 104-week carcinogenicity studies conducted on both rats and mice. The studies showed a duration and dose-dependent increase in C-cell carcinomas. The statistically significant increase risk was evident in both sexes of rodents, but males showed a higher rate. All of the clinical trials reported four cases of thyroid C-cell tumors for human patients using liraglutide, while comparators had one reported case. Based on current evidence the FDA was unable to determine if the increased risk actually translates to humans. Liraglutide is contraindicated in patients diagnosed with or having a family history of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2).[4,9]

The total frequency of withdrawal as a result of side effects was 7.8% during phase III clinical trials.[PI] The majority of these patients withdrew due to gastrointestinal adverse events. The most commonly reported adverse events during monotherapy were nausea, diarrhea, vomiting, and constipation (**Table 3**).[7,8] Table 3 provides a summary of the most common adverse events during the relevant clinical trials.

Dosing & Administration

Liraglutide is approved for once daily subcutaneous administration. The available injection sites are the abdomen, the upper thigh, and the upper arm. Liraglutide comes as a pre-filled, disposable, multi-dose pen. Each pen contains 3 mL of solution, and the concentration is 6 mg/mL. Patients can give the injection without regards to meals or the time of day. The starting dose is 0.6 mg once daily for the first week to lessen the gastrointestinal side effects. After one week, the dose should be increased to 1.2 mg daily. If 1.2 mg is not providing effective glycemic control, it can be increased to the maximum dose of 1.8 mg once daily.[4]

Cost

The available pack sizes for Victoza® are two pens and three pens. The average price for two pens is $291.63 ($283.95-$302.95) and the average price for the three-pen pack is $469.62 ($435.95-$515.95). These prices represent the monthly cost for patients on 1.2 mg once daily and 1.8 mg once daily respectively.

Summary

Liraglutide, a new GLP-1 receptor agonist, provides clinicians an alternative to current DM treatment options. This agent proved safe and effective as monotherapy and as an add-on to current treatment options when used with diet and exercise for glycemic control. Liraglutide provides convenient once daily dosing, has relatively few drug interactions, causes a clinically significant reduction in A_{1c} with minimal hypoglycemia, and potentially reduces body weight.

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PITAVASTATIN: A NEW STATIN TO TREAT HYPERLIPIDEMIA

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The American Heart Association estimates that 102.3 million American adults have total blood cholesterol levels of 200 mg/dl or higher.[1] The main aim of anti-hyperlipidemic therapy is a reduction in low density lipoprotein cholesterol (LDL-C) which is a significant cardiovascular risk factor. Moreover, studies have shown for every one percent reduction in LDL cholesterol there is a one percent reduction in CHD events.[2] Due to the superior LDL lowering efficacy of statins as compared to other therapies, this class of medications is considered first line treatment for hyperlipidemia.[3] In August 2009, the Food and Drug Administration approved another statin pitavastatin (Livalo®) which is manufactured by Kowa phar-

Table 1. Pharmacokinetics of Pitavastatin.[4]

Property	Pitavastatin
Volume of Distribution	148 L
Protein Binding	> 99%
Bioavailability	51%
Time to peak in serum	1 hour
Elimination Half life	12 hours
Metabolism	Primarily UGT 1A3 and UGT 2B7 small extent CYP2C8, CYP 2C9
Excretion	79% fecal 15% urine

Table 2. Mean Percent Change from Baseline to Week 12 in Dose-Ranging Studies.[4]

Treatment	N	LDL	Apo-B	TG	TC	HDL
Placebo	53	-3	-2	1	-2	0
Pitavastatin 1mg	52	-32	-25	-15	-23	8
Pitavastatin 2mg	49	-36	-30	-19	-26	7
Pitavastatin 4 mg	51	-43	-35	-18	-31	5

maceuticals. Although new to the United States this statin has been in use in Asian countries since 2003. The intent of this article is to discuss the pharmacology, pharmacokinetics, efficacy, and safety of pitavastatin.

Pharmacology

Similar to the other currently available statins, pitavastatin affects the rate limiting step of cholesterol synthesis by inhibiting HMG-CoA reductase. Pitavastatin is approved as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), triglycerides (TG), and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hyperlipidemia and mixed dyslipidemia.[4]

Pharmacokinetics

The main pharmacokinetic parameters of pitavastatin are summarized in **Table 1**. Pitavastatin undergoes carrier-mediated uptake in hepatocytes by organic anionic transporting polypeptide 1B1.[5] Pitavastatin undergoes hepatic metabolism primarily by UGT metabolism (UGT1A3 and UGT2B7) and minimally CYP-mediated (CYP2C9 and CYP2C8). This property may reduce the occurrence of drug-drug interactions. However, non-CYP-mediated metabolism does not make pitavastatin unique for other statins (pravastatin and rosuvatatin) also share this characteristic.

Clinical Trials

Dose-Ranging Study

A multicenter randomized, double- blind, placebo-controlled study involving 251 participants with primary hyperlipidemia was performed to ascertain appropriate dosing.[4] Participants were given pitavastatin or matching placebo once daily for 12 weeks. The effects on LDL, TC, TG, Apo-B and HDL are summarized below in Table 2. At a dose of pitavastatin 1 mg daily the average reduction in LDL was 32% (**Table 2**).[4]

Pitavastatin vs. Atorvastatin

During a phase 3 trial pitavastatin was compared to atorvastatin in a randomized, multicenter, double-blind, active comparator, non-inferiority study. The study included 817 participants with primary hyperlipidemia or mixed dyslipidemia. All of the participants first underwent a 6-8 week washout period. The participants were then assigned to either pitavastatin 2 mg, pitavastatin 4mg, atorvastatin 10mg or atorvastatin 20 mg daily for 12 weeks. Non-inferiority was demonstrated for both pitavastatin 2 mg vs. atorvastatin 10 mg and pitavastatin 4 mg vs. atorvastatin 20 mg (**Tables 3 & 4**).[4]

Pitavastatin vs. Simvastatin

A similar study by Ose et al. compared the effects of pitavastatin against simvastatin in participants with primary hypercholesterolemia or combined dyslipide-

Table 3. Mean Percent Change in Lipid Parameters for Pitavastatin vs. Atorvastatin from Baseline to Week 12.[4]

Parameter	Pitavastatin 2 mg (n=315)	Atorvastatin 10 mg (n=102)	Pitavastatin 4 mg (n=298)	Atorvastatin 20 mg (n=102)
LDL-C	-38	-38	-45	-44
TC	-28	-28	-32	-33
TG	-14	-18	-19	-22
HDL-C	4	3	5	2

Table 4. Summary of Pitavastatin Clinical Trials.[4-9]

REFERENCE	DESIGN	RESULTS
Package Insert[4]	• 12 week, R, DB, NI • Participants with primary Hyperlipidemia or mixed dyslipidemia (N=817) • Primary endpoint: Mean treatment differences in LDL-C reduction	No difference in LDL-C reduction between pitavastatin 2 mg vs. atorvastatin 10mg or between pitavastatin 4 mg vs. atorvastatin 20 mg.
Package Insert[4]	• 12 week, R,M, DB, DD, AC, NI • Participants with Dyslipidemia and 2 or more coronary risk factors (N=351) • Primary endpoint: LDL-C reduction	No difference in LDL-C reduction between pitavastatin 4mg (44% reduction) vs. simvastatin 40 mg (44% reduction)
Package Insert[4]	• 12 week, R,M, DB,DD,AC, NI • Participants with Dyslipidemia and Type 2 DM (N=410) • Primary endpoint: Mean LDL-C% change from baseline at Week 12	Significantly greater reduction in LDL-C for atorvastatin 20 mg (43% reduction) vs. pitavastatin 4 mg (41% reduction)
Saito (2002)[5,7]	• 12 week, R, DB, AC • Participants with Primary Hyperlipidemia (N=236) • Primary endpoint: Percent change in TC, LCL-C, and TG	Significantly greater reduction in TC (additional 14% reduction) and LDL-C (additional 18.4% reduction) with pitavastatin 2 mg compared with pravastatin 10 mg ; p<0.001
Park (2005)[5,8]	• 8 week, OL, AC • Participants with Hypercholesterolemia (N=95) • Primary endpoint: LDL-C% change	No significant difference between % change in LDL-C for pitavastatin 2 mg (38.2% reduction) vs. simvastatin 20 mg (39.4% reduction)
Lee (2007)[5,9]	• 8 week, R, OL,AC • Participants with Hypercholesterolemia (N=268) • Primary endpoint: Proportion of participants achieving LDL-C goal	No significant difference in proportion of patients achieving LDL-C goal between pitavastatin 2 mg (92.7% of patients) vs. atorvastatin 10 mg (92% of patients)
Sasaki (2008)[5]	• 52 week, R, OL, AC • Participants with elevated LDL-density lipoprotein and glucose intolerance (N=207) • Primary endpoint:HDL-C% change	Significantly greater increase in HDL-C with pitavastatin 2 mg daily (8.2% increase) vs. atorvastatin 10 mg daily (2.9% increase); p=0.031
Ose (2009)[6]	• 12 week, P, R, AC, DB, DD, NI • Participants with primary Hypercholesterolemia or mixed dyslipidemia (N=843) • Primary endpoint: LDL-C reduction	No significant difference in LDL-C reduction between pitavastatin 2 mg (39% reduction) vs. simvastatin 20 mg (35% reduction) or between pitavastatin 4 mg (44% reduction) vs. simvastatin 40 mg (43% reduction)

AC = active controlled; **DB** = double-blind; **DD** = double-dummy; **M** = multicenter; **NI** = non-inferiority; **OL** = open-label; **P** = prospective; **R** = randomized.

mia (**Table 4**). The study was a prospective, randomized, active-controlled, double-blind, double-dummy trial which lasted 12 weeks. Eligible participants were men and women (non-pregnant and non-lactating) aged 18-75 years. The study enrolled 857 participants. Prior to randomization, participants followed the European Atherosclerosis Society diet for 6 weeks. Participants receiving previous lipid-lowering therapy underwent a wash-out period and followed the diet for 8 weeks prior to randomization. At the end of the diet participants were diagnosed with hyperlipidiemia if LDL-C levels were ≥160 mg/dl and ≤ 220 mg/dl and

Table 5. Adverse Reactions Reported by >2.0% of Participants Treated with Pitavastatin and Placebo.[4]

Adverse Reactions	Placebo (n=208)	Pitavastatin 1 mg (n=309)	Pitavastatin 2 mg (n=951)	Pitavastatin 4 mg (n=1540)
Myalgia	1.4%	1.9%	2.8%	3.1%
Pain in Extremity	1.9%	2.3%	0.6%	0.9%
Diarrhea	1.9%	2.6%	1.5%	1.9%
Constipation	1.9%	3.6%	1.5%	1.9%
Back Pain	2.9%	3.9%	1.8%	1.4%

mean trigelyceride levels were ≤ 400 mg/dl. The participants who met this criteria were allocated in a 3:3:1:1 ratio to treatment with pitavastatin 2 mg/day, pitavastatin 4 mg/day, simvastatin 20 mg/day, or simvastatin 40mg/day. Mean LDL levels were reduced by 39% in the pitavastatin 2 mg group, 35% in the simvastatin 20 mg group, 44% in the pitavastatin 4 mg group, and 43% in the simvastatin 40 mg group. The authors concluded pitavastatin to be noninferioir to simvastatin and found the adverse event profiles to be similar. Musculoskeletal and gastrointestinal side effects were the most common reason for discontinuation for both agents.[5]

Adverse Reactions

Myaligia is the most common adverse event experienced by participants treated with pitavastatin (**Table 5**). Other reported adverse reactions include arthralgia, headache, influenza, nasopharyngitis, and hypersensitivity reactions such as rash and pruritus.

Pitavastatin may lead to laboratory abnormalities such as elevated creatine phosphokinse, glucose, alkaline phosphatase, bilirubin, and transaminases.

Drug Interactions

Although pitavastatin undergoes minimal CYP-mediated metabolism significant drug interactions still exist. Several medications can increase the AUC of pitavastatin. The manufacturer recommends avoiding concomitant use of the anti-retroviral drugs lopinvir/ritonavir if possible. Likewise, when co-administering erythromycin therapy, the pitavastatin dose should be limited to 1 mg daily.

As with other statins, combination therapy with fibrates and niacin can lead to an increased risk of musculoskeletal side effects. The manufacturer does suggest a reduction in pitavastatin dosing when initiating niacin therapy and suggests using caution with fibrate therapy.

As mentioned previously, pitavastatin is metabolized to a small extent by the enzyme CYP2C9 which is responsible for the majority of warfarin metabolism. Participants receiving concomitant pitavastatin and warfarin therapy in clinical trials did not have a significant altered INR or PT. However, the manufacturer suggests monitoring patients PT and INR when initiating pitavastatin.[4]

Dosing & Precautions

Pitavastatin is available in 1 mg, 2 mg, and 4 mg tablets.[4] The pricing information has not yet been published. Pitavastatin will likely provide little economic benefit considering the brand- only status of the medication and the availability of several generic statins.[5]

Pitavastatin can be administered anytime of the day with or without food. Daily doses should not exceed 4 mg due to an association with an increased risk of severe myopathy.

Pitavastatin is contraindicated in patients receiving cyclosporine. When participants on 2mg of pitavastatin were administered 2 mg/kg of cyclosporine for 6 days, the Cmax of pitavastatin increased by 6.6-fold. Pitavastatin is also contraindicated in patients with active liver disease and those with unexplained persistent elevations of serum transaminases.

Like other members of the statin class, pitavastatin is a category X during pregnancy and therapy should be discontinued. Pitavastatin has not been shown to be excreted in breast milk. However, the manufacturer recommends against breastfeeding or to consider alternative therapies.[4]

Renal dose adjustments are necessary for this medication. Patients with moderate renal impairment or end-stage renal disease should receive a lower starting dose of 1 mg daily and should not exceed a maximum dose of 2 mg daily. In patients who are not receiving dialysis with creatinine clearances of less

than 30 ml/min the use of pitavastatin is not recommended for this population has not yet been studied.[4]

SUMMARY

Statin therapy remains first line for patients with hyperlipidemia.[3] Pitavastatin is the newest member of this class. This agent has similar efficacy to low-to-moderate doses of both atorvastatin and simvastatin when comparing LDL-C reduction. However, data showing a reduction in mortality and CHD remains to be seen.[4] Pitavastatin undergoes both minimal CYP - mediated metabolism and renal elimination. However, as already discussed these features are not unique to this agent. Also, due to the brand only status of this medication it is unlikely to be less expensive than currently available generic statins. Overall, the exact role of this statin in clinical practice may be limited due to all of these factors.

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