HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYPITAMAG safely and effectively. See full prescribing information for ZYPITAMAG.

ZYPITAMAG (pitavastatin) tablets, for oral use
Initial U.S. Approval: 2009

---------------------------INDICATIONS AND USAGE----------------------------

ZYPITAMAG is an HMG-CoA reductase inhibitor indicated for:

- Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) (1.1)

Limitations of Use (1.2):

- Doses greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing.
- The effect of ZYPITAMAG on cardiovascular morbidity and mortality has not been determined.
- ZYPITAMAG has not been studied in Fredrickson Type I, III, and V dyslipidemias.

----------------------DOSAGE AND ADMINISTRATION-------------------------

- Can be taken with or without food, at any time of day (2.1)
  Dose Range: 1 mg to 4 mg once daily (2.1)
- *Primary hyperlipidemia and mixed dyslipidemia*: Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day. (2.1)
- *Moderate and severe renal impairment and end-stage renal disease on hemodialysis*: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily (2.2)

---------------------DOSAGE FORMS AND STRENGTHS------------------------

Tablets: 1 mg, 2 mg and 4 mg (3)

----------------------------CONTRAINDICATIONS-----------------------------------

- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Pregnancy (4, 8.1, 8.3)
- Lactation (4, 8.2)
- Coadministration with cyclosporine (4, 7.1, 12.3)

------------------------WARNINGS AND PRECAUTIONS--------------------------

- *Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):* Risks increase in a dose-dependent manner, with advanced age (≥ 65), renal impairment, and inadequately treated hypothyroidism. Advise patients to promptly report unexplained and/or persistent muscle pain, tenderness, or weakness, and discontinue ZYPITAMAG (5.1)
- *Liver enzyme abnormalities:* Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2)

-----------------------------ADVERSE REACTIONS-----------------------------------

The most frequent adverse reactions (rate ≥ 2% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------------------------------DRUG INTERACTIONS--------------------------------

- *Erythromycin:* Combination increases pitavastatin exposure. Limit ZYPITAMAG to 1 mg once daily (2.3, 7.2)
- *Rifampin:* Combination increases pitavastatin exposure. Limit ZYPITAMAG to 2 mg once daily (2.4, 7.3)
- *Concomitant lipid-lowering therapies:* Use with fibrates or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with ZYPITAMAG. (5.1, 7.4, 7.5)

---------------------USE IN SPECIFIC POPULATIONS----------------------------

- *Females and Males of Reproductive Potential:* Advise females to use effective contraception during treatment. (8.3)
- *Pediatric use:* Safety and effectiveness have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Drug therapy should be one component of multiple-risk-factor intervention in individuals who require modifications of their lipid profile. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate.

1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

ZYPITAMAG is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

1.2 Limitations of Use

Doses of ZYPITAMAG greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of ZYPITAMAG.

The effect of ZYPITAMAG on cardiovascular morbidity and mortality has not been determined.

ZYPITAMAG has not been studied in Fredrickson Type I, III, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for ZYPITAMAG is 1 mg to 4 mg orally once daily at any time of the day with or without food. The recommended starting dose is 2 mg and the maximum dose is 4 mg. The starting dose and maintenance doses of ZYPITAMAG should be individualized according to patient characteristics, such as goal of therapy and response.

After initiation or upon titration of ZYPITAMAG, lipid levels should be analyzed after 4 weeks and the dosage adjusted accordingly.

2.2 Dosage in Patients with Renal Impairment

Patients with moderate and severe renal impairment (glomerular filtration rate 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2 and 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2 not receiving hemodialysis, respectively) as well as end-stage renal disease receiving hemodialysis should receive a starting dose of ZYPITAMAG 1 mg once daily and a maximum dose of ZYPITAMAG 2 mg once daily.

2.3 Use with Erythromycin

In patients taking erythromycin, a dose of ZYPITAMAG 1 mg once daily should not be exceeded *[see Drug Interactions (7.2)]*.

2.4 Use with Rifampin

In patients taking rifampin, a dose of ZYPITAMAG 2 mg once daily should not be exceeded *[see Drug Interactions (7.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- 1 mg: White to off-white, beveled-edge, round-shaped tablets debossed with “876” on one side and plain on the other side.
- 2 mg: White to off-white, beveled-edge, round-shaped tablets debossed with “877” on one side and plain on the other side.

- 4 mg: White to off-white, beveled-edge, round-shaped tablets debossed with “878” on one side and plain on the other side.

4 CONTRAINDICATIONS

The use of ZYPITAMAG is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with pitavastatin *[see Adverse Reactions (6.1)]*.
- Patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.
- Coadministration with cyclosporine *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.
- Pregnancy. *[see Use in Specific Populations (8.1, 8.3)]*.
- Lactation. It is not known if ZYPITAMAG is present in human milk; however, another drug in this class passes into breast milk. Since HMG-CoA reductase inhibitors have the potential for serious adverse reactions in breastfed infants, women who require ZYPITAMAG treatment should not breastfeed their infants *[see Use in Specific Populations (8.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including pitavastatin. These risks can occur at any dose level, but increase in a dose-dependent manner.

ZYPITAMAG should be prescribed with caution in patients with predisposing factors for myopathy. These factors include advanced age (≥ 65 years), renal impairment, and inadequately treated hypothyroidism. The risk of myopathy may also be increased with concurrent administration of fibrates or lipid-modifying doses of niacin. ZYPITAMAG should be administered with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin *[see Drug Interactions (7.6), Use in Specific Populations (8.5, 8.6) and Clinical Pharmacology (12.3)]*.

Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors coadministered with colchicine, and caution should be exercised when prescribing ZYPITAMAG with colchicine [*see Drug Interactions (7.7)*].

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

ZYPITAMAG therapy should be discontinued if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. ZYPITAMAG therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ZYPITAMAG.

5.2 Liver Enzyme Abnormalities

Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including pitavastatin. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

In placebo-controlled Phase 2 studies, ALT > 3 times the upper limit of normal was not observed in the placebo, pitavastatin 1 mg, or pitavastatin 2 mg groups. One out of 202 patients (0.5%) administered pitavastatin 4 mg had ALT > 3 times the upper limit of normal.

It is recommended that liver enzyme tests be performed before the initiation of ZYPITAMAG and if signs or symptoms of liver injury occur.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with ZYPITAMAG, promptly interrupt therapy. If an alternate etiology is not found do not restart ZYPITAMAG.

As with other HMG-CoA reductase inhibitors, ZYPITAMAG should be used with caution in patients who consume substantial quantities of alcohol. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of ZYPITAMAG *[see Contraindications (4)]*.

5.3 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including pitavastatin.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) *[see Warnings and Precautions (5.1)]*.
- Liver Enzyme Abnormalities *[see Warning and Precautions (5.2)]*.

Of 4,798 patients enrolled in 10 controlled clinical studies and 4 subsequent open-label extension studies, 3,291 patients were administered pitavastatin 1 mg to 4 mg daily. The mean continuous exposure of pitavastatin (1 mg to 4 mg) was 36.7 weeks (median 51.1 weeks). The mean age of the patients was 60.9 years (range; 18 years to 89 years) and the gender distribution was 48% males and 52% females. Approximately 93% of the patients were Caucasian, 7% were Asian/Indian, 0.2% were African American and 0.3% were Hispanic and other.

6.1 Clinical Studies Experience

Because clinical studies on pitavastatin are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of pitavastatin cannot be directly compared with that in the clinical studies of other HMG-CoA reductase inhibitors and may not reflect the frequency of adverse reactions observed in clinical practice.

Adverse reactions reported in ≥ 2% of patients in controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had treatment duration of up to 12 weeks.

Table 1 Adverse Reactions* Reported by ≥ 2% of Patients Treated with Pitavastatin and > Placebo in Short-Term Controlled Studies

Adverse Reactions*	Placebo N= 208	Pitavastatin 1 mg N=309	Pitavastatin 2 mg N=951	Pitavastatin 4 mg N=1540
Back Pain	2.9%	3.9%	1.8%	1.4%
Constipation	1.9%	3.6%	1.5%	2.2%
Diarrhea	1.9%	2.6%	1.5%	1.9%
Myalgia	1.4%	1.9%	2.8%	3.1%
Pain in extremity	1.9%	2.3%	0.6%	0.9%

* Adverse reactions by MedDRA preferred term.

Other adverse reactions reported from clinical studies were arthralgia, headache, influenza, and nasopharyngitis.

The following laboratory abnormalities have also been reported: elevated creatine phosphokinase, transaminases, alkaline phosphatase, bilirubin, and glucose.

In controlled clinical studies and their open-label extensions, 3.9% (1 mg), 3.3% (2 mg), and 3.7% (4 mg) of pitavastatin-treated patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: elevated creatine phosphokinase (0.6% on 4 mg) and myalgia (0.5% on 4 mg).

Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with pitavastatin.

In a double-blind, randomized, controlled, 52-week trial, 252 HIV-infected patients with dyslipidemia were treated with either pitavastatin 4mg once daily (n=126) or another statin (n=126). All patients were taking antiretroviral therapy (excluding darunavir) and had HIV-1 RNA less than 200 copies/mL and CD4 count greater than 200 cell/μL for at least 3 months prior to randomization. The safety profile of pitavastatin was generally consistent with that observed in the clinical trials described above. One patient (0.8%) treated with pitavastatin had a peak creatine phosphokinase value exceeding 10 times the upper limit of normal (10x ULN), which resolved spontaneously. Four patients (3%) treated with pitavastatin had at least one ALT value exceeding 3x but less than 5x ULN, none of which led to drug discontinuation. Virologic failure was reported for four patients (3%) treated with pitavastatin, defined as a confirmed measurement of HIV-1 RNA exceeding 200 copies/mL that was also more than a 2-fold increase from baseline.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of pitavastatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with pitavastatin therapy reported since market introduction, regardless of causality assessment, include the following: abdominal discomfort, abdominal pain, dyspepsia, nausea, asthenia, fatigue, malaise, hepatitis, jaundice, fatal and non-fatal hepatic failure, dizziness, hypoesthesia, insomnia, depression, interstitial lung disease, erectile dysfunction, muscle spasms and peripheral neuropathy.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Cyclosporine
Cyclosporine significantly increased pitavastatin exposure. Coadministration of cyclosporine with ZYPITAMAG is contraindicated [*see Contraindications (4), and Clinical Pharmacology (12.3)]*.

7.2 Erythromycin
Erythromycin significantly increased pitavastatin exposure. In patients taking erythromycin, a dose of ZYPITAMAG 1 mg once daily should not be exceeded *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.3 Rifampin
Rifampin significantly increased pitavastatin exposure. In patients taking rifampin, a dose of ZYPITAMAG 2 mg once daily should not be exceeded *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

7.4 Gemfibrozil
Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of ZYPITAMAG with gemfibrozil should be avoided.

7.5 Other Fibrates
Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, ZYPITAMAG should be administered with caution when used concomitantly with other fibrates *[see Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

7.6 Niacin
The risk of skeletal muscle effects may be enhanced when ZYPITAMAG is used in combination with niacin; a reduction in ZYPITAMAG dosage should be considered in this setting *[see Warnings and Precautions (5.1)]*.

7.7 Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors coadministered with colchicine, and caution should be exercised when prescribing ZYPITAMAG with colchicine.

7.8 Warfarin
Pitavastatin had no significant pharmacokinetic interaction with R- and S- warfarin. Pitavastatin had no significant effect on prothrombin time (PT) and international normalized ratio (INR) when administered to patients receiving chronic warfarin treatment *[see Clinical Pharmacology (12.3)]*. However, patients receiving warfarin should have their PT and INR monitored when ZYPITAMAG is added to their therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ZYPITAMAG is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit to therapy with pitavastatin during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ZYPITAMAG may cause fetal harm when administered to pregnant women. ZYPITAMAG should be discontinued as soon as pregnancy is recognized *[see Contraindications (4)]*. Limited published data on the use of pitavastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no embryo-fetal toxicity or congenital malformations were observed when pregnant rats and rabbits were orally administered pitavastatin during organogenesis at exposures which were 22 times and 4 times, respectively, the maximum recommended human dose (MRHD) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Limited published data on pitavastatin have not reported a drug-associated risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. The number of cases is adequate to exclude a greater than or equal to a 3-to 4-fold increase in congenital anomalies over background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Animal Data

Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤ 36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation.

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3 mg/kg/day, 10 mg/kg/day, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.
Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1 mg/kg/day, 0.3 mg/kg/day, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

In perinatal/postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 0.1 mg/kg/day, 0.3 mg/kg/day, 1 mg/kg/day, 3 mg/kg/day, 10 mg/kg/day, 30 mg/kg/day from organogenesis through weaning, maternal toxicity consisting of mortality at ≥ 0.3 mg/kg/day and impaired lactation at all doses contributed to the decreased survival of neonates in all dose groups (0.1 mg/kg/day represents approximately 1 time human systemic exposure at 4 mg/day dose based on AUC).

8.2 Lactation

Risk Summary

ZYPITAMAG is contraindicated during breastfeeding *[see Contraindications (4.4)]*. There is no information about the presence of pitavastatin in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in this class passes into human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ZYPITAMAG.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ZYPITAMAG may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYPITAMAG.

8.4 Pediatric Use

Safety and effectiveness of ZYPITAMAG in pediatric patients have not been established.

8.5 Geriatric Use

Of the 2,800 patients randomized to pitavastatin 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were 65 years and older. No significant differences in efficacy or safety were observed between elderly patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Patients with moderate and severe renal impairment (glomerular filtration rate 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2 and 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2 not receiving hemodialysis, respectively) as well as end-stage renal disease receiving hemodialysis should receive a starting dose of ZYPITAMAG 1 mg once daily and a maximum dose of ZYPITAMAG 2 mg once daily *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

ZYPITAMAG is contraindicated in patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels.

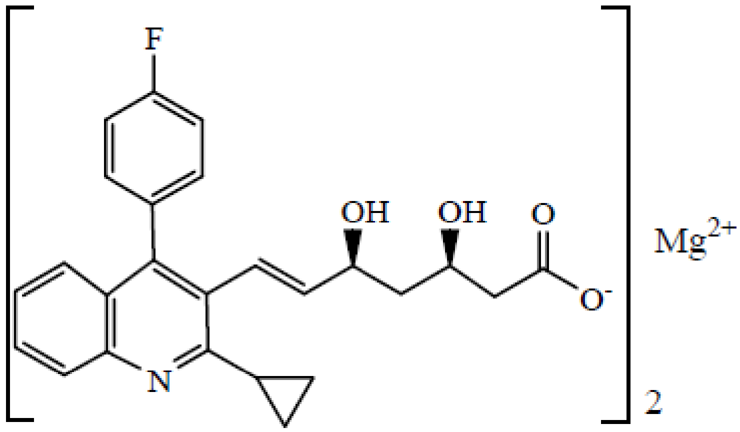
10 OVERDOSAGE

There is no known specific treatment in the event of overdose of pitavastatin. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis is unlikely to be of benefit due to high protein binding ratio of pitavastatin.

11 DESCRIPTION

ZYPITAMAG (pitavastatin) is an inhibitor of HMG-CoA reductase. It is a synthetic lipid-lowering agent for oral administration.

The chemical name for pitavastatin is (3R,5S)-7-[2-Cyclopropyl-4-(4-fluorophenyl) quinoline-3-yl]3,5-dihydroxy-6(E)-heptanoic acid hemi magnesium. The structural formula is:



The molecular formula for pitavastatin is $C_{50}H_{46}MgF_2N_2O_8$ and the molecular weight is 865.21. Pitavastatin is a white to off-white powder. It is freely soluble in acetone, ethyl acetate; soluble in dimethylsulfoxide and insoluble in dichloromethane and isopropyl alcohol. Pitavastatin is hygroscopic and slightly unstable in light.

Each film-coated tablet of ZYPITAMAG contains 1.026 mg, 2.053 mg, or 4.106 mg of pitavastatin magnesium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base and the following inactive ingredients: calcium carbonate, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and sodium carbonate anhydrous and film- coating containing the following inactive ingredients: hypromellose, polyethylene glycol, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins.

12.2 Pharmacodynamics

In a randomized, double-blind, placebo-controlled, 4-way parallel, active-comparator study with moxifloxacin in 174 healthy participants, pitavastatin was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 16 mg (4 times the recommended maximum daily dose).

12.3 Pharmacokinetics

Absorption

Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both C_{max} and $AUC_{0\text{-}inf}$ increased in an approximately dose-proportional manner for single pitavastatin doses from 1 mg to 24 mg once daily. The absolute bioavailability of pitavastatin oral solution is 51%. Administration of a 4 mg ZYPITAMAG tablet with a high fat meal (50% fat content) decreases pitavastatin C_{max} by 39% but does not significantly reduce pitavastatin AUC. The C_{max} and AUC of pitavastatin did not differ following evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the percent change from baseline for LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the small intestine but very little in the colon.

Distribution

Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells is minimal.

Metabolism

Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite in human plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uridine 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion

A mean of 15% of radioactivity of orally administered, single 32 mg ^{14}C-labeled pitavastatin dose was excreted in urine, whereas a mean of 79% of the dose was excreted in feces within 7 days. The mean plasma elimination half-life is approximately 12 hours.

Race

In pharmacokinetic studies pitavastatin C_{max} and AUC were 21 and 5% lower, respectively in Black or African American healthy volunteers compared with those of Caucasian healthy volunteers. In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in C_{max} and AUC.

Gender

In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C_{max} and AUC were 60 and 54% higher, respectively in females. This had no effect on the efficacy or safety of pitavastatin in women in clinical studies.

Geriatric

In a pharmacokinetic study which compared healthy young and elderly (≥ 65 years) volunteers, pitavastatin C_{max} and AUC were 10 and 30% higher, respectively, in the elderly. This had no effect on the efficacy or safety of pitavastatin in elderly subjects in clinical studies.

Renal Impairment

In patients with moderate renal impairment (glomerular filtration rate of 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2) and end stage renal disease receiving hemodialysis, pitavastatin $AUC_{0\text{-}inf}$ is 102 and 86% higher than those of healthy volunteers, respectively, while pitavastatin C_{max} is 60 and 40% higher than those of healthy volunteers, respectively. Patients received hemodialysis immediately before pitavastatin dosing and did not undergo hemodialysis during the pharmacokinetic study. Hemodialysis patients have 33 and 36% increases in the mean unbound fraction of pitavastatin as compared to healthy volunteers and patients with moderate renal impairment, respectively.

In another pharmacokinetic study, patients with severe renal impairment (glomerular filtration rate 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2) not receiving hemodialysis were administered a single dose of pitavastatin 4 mg. The $AUC_{0\text{-}inf}$ and the C_{max} were 36 and 18% higher, respectively, compared with those of healthy volunteers. For both patients with severe renal impairment and healthy volunteers, the mean percentage of protein-unbound pitavastatin was approximately 0.6%.

The effect of mild renal impairment on pitavastatin exposure has not been studied.

Hepatic Impairment

The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. The ratio of pitavastatin C_{max} between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers was 2.7. The ratio of pitavastatin AUC_{inf} between patients with moderate hepatic impairment and healthy volunteers was 3.8. The ratio of pitavastatin C_{max} between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteers was 1.3. The ratio of pitavastatin AUC_{inf} between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean pitavastatin $t_{½}$ for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively.

Drug-Drug Interactions

The principal route of pitavastatin metabolism is glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system.

Warfarin

The steady-state pharmacodynamics (international normalized ratio [INR] and prothrombin time [PT]) and pharmacokinetics of warfarin in healthy volunteers were unaffected by the coadministration of pitavastatin 4 mg daily. However, patients receiving warfarin should have their PT time or INR monitored when ZYPITAMAG is added to their therapy.

Table 2 Effect of Coadministered Drugs on Pitavastatin Systemic Exposure

Coadministered drug	Dose regimen	Change in AUC*	Change in C_{max}*
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Darunavir/Ritonavir	Pitavastatin 4 mg QD on Days 1 to 5 and 12 to 16 + darunavir/ritonavir 800 mg/100 mg QD on Days 6 to 16	↓ 26%	↓ 4%
Lopinavir/Ritonavir	Pitavastatin 4 mg QD on Days 1 to 5 and 20 to 24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 to 24	↓ 20%	↓4 %
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1 to 5 and 11 to 15 and diltiazem LA 240 mg on Days 6 to 15	↑10%	↑15%

Coadministered drug	Dose regimen	Change in AUC*	Change in C_{max}*
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days	↑ 15%	↓ 12%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

*Data presented as x-fold change represent the ratio between coadministration and pitavastatin alone (i.e., 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).
† Considered clinically significant *[see Dosage and Administration (2) and Drug Interactions (7)]*
BID = twice daily; QD = once daily; LA = Long Acting

Table 3 Effect of Pitavastatin Coadministration on Systemic Exposure to Other Drugs

Coadministered drug	Dose regimen		Change in AUC*	Change in C_{max} *
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Darunavir	Pitavastatin 4 mg QD on Days 1 to 5 and 12 to 16 + darunavir/ritonavir 800 mg/100 mg QD on Days 6 to 16		↑ 3%	↑ 6%
Lopinavir	Pitavastatin 4 mg QD on Days 1 to 5 and 20 to 24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 to 24		↓ 9%	↓ 7%
Ritonavir	Pitavastatin 4 mg QD on Days 1 to 5 and 20 to 24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 to 24		↓ 11%	↓ 11%
Ritonavir	Pitavastatin 4 mg QD on Days 1 to 5 and 12 to 16 + darunavir/ritonavir 800 mg/100 mg QD on Days 6 to 16		↑ 8%	↑ 2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	Enalapril	↑ 12%	↑ 12%
		Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 to 7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑ 7%	↑ 3%
		S-warfarin	↑ 6%	↑ 3%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days		↑ 9%	↑ 2%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days		↓ 3%	↓ 4%

Coadministered drug	Dose regimen	Change in AUC*	Change in C_{max} *
Diltiazem LA	Pitavastatin 4 mg QD on Days 1 to 5 and 11 to 15 and diltiazem LA 240 mg on Days 6 to 15	↓ 2%	↓ 7%
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↓ 15%	↓ 18%

Data presented as % change represent % difference relative to the investigated drug alone (i.e., 0% = no change).
BID = twice daily; QD = once daily; LA = Long Acting

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 92 week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors.

In a 92 week carcinogenicity study in rats given pitavastatin at 1 mg/kg/day, 5 mg/kg/day, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.

In a 26 week transgenic mouse (Tg rasH2) carcinogenicity study where animals were given pitavastatin at 30 mg/kg/day, 75 mg/kg/day, and 150 mg/kg/day by oral gavage, no clinically significant tumors were observed.

Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rats, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test, clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity.

Pitavastatin had no adverse effects on male and female rat fertility at oral doses of 10 mg/kg/day and 30 mg/kg/day, respectively, at systemic exposures 56 and 354 times clinical exposure at 4 mg/day based on AUC. Pitavastatin treatment in rabbits resulted in mortality in males and females given 1 mg/kg/day (30 times clinical systemic exposure at 4 mg/day based on AUC) and higher during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened) indicative of possible ischemia. Lower doses (15 times human systemic exposure) did not show significant toxicity in adult males and females. However, decreased implantations, increased resorptions, and decreased viability of fetuses were observed.

13.2 Animal Toxicology and/or Pharmacology

Central Nervous System Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Wallerian degeneration has not been observed with pitavastatin. Cataracts and lens opacities were seen in dogs treated for 52 weeks at a dose level of 1 mg/kg/day (9 times clinical exposure at the maximum human dose of 4 mg/day based on AUC comparisons).

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia or Mixed Dyslipidemia

Dose-ranging study:

A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study was performed to evaluate the efficacy of pitavastatin compared with placebo in 251 patients with primary hyperlipidemia (Table 4). Pitavastatin, given as a single daily dose for 12 weeks, significantly reduced plasma LDL-C, TC, TG, and Apo-B compared to placebo and was associated with variable increases in HDL-C across the dose range.

Table 4 Dose-Response in Patients with Primary Hypercholesterolemia (Adjusted Mean % Change from Baseline at Week 12)

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

The number of subjects for Apo-B was 49

Active-controlled study with atorvastatin (NK-104-301)

Pitavastatin was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 817 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6 to 8 week wash-out/dietary lead-in period and then were randomized to a 12 week treatment with either pitavastatin or atorvastatin (Table 5). Non-inferiority of pitavastatin to a given dose of atorvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 5. For the percent change from baseline to endpoint in LDL-C, pitavastatin was non-inferior to atorvastatin for the two pairwise comparisons: pitavastatin 2 mg vs. atorvastatin 10 mg and pitavastatin 4 mg vs. atorvastatin 20 mg. Mean treatment differences (95% CI) were 0% (-3%, 3%) and 1% (-2%, 4%), respectively.

Table 5 Response by Dose of Pitavastatin and Atorvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
Pitavastatin 2 mg daily	315	-38	-30	-28	-14	4	-35
Pitavastatin 4 mg daily	298	-45	-35	-32	-19	5	-41
Atorvastatin 10 mg daily	102	-38	-29	-28	-18	3	-35
Atorvastatin 20 mg daily	102	-44	-36	-33	-22	2	-41
Atorvastatin 40 mg daily	--Not Studied-----------------------------------						
Atorvastatin 80 mg daily	--Not Studied-----------------------------------						

Active-controlled study with simvastatin (NK-104-302)

Pitavastatin was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 843 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6 to 8 week wash-out/dietary lead-in period and then were randomized to a 12 week treatment with either pitavastatin or simvastatin (Table 6). Non-inferiority of pitavastatin to a given dose of simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 6. For the percent change from baseline to endpoint in LDL-C, pitavastatin was non-inferior to simvastatin for the two pairwise comparisons: pitavastatin 2 mg vs. simvastatin 20 mg and pitavastatin 4 mg vs. simvastatin 40 mg. Mean treatment differences (95% CI) were 4% (1%, 7%) and 1% (-2%, 4%), respectively.

Table 6 Response by Dose of Pitavastatin and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
Pitavastatin 2 mg daily	307	-39	-30	-28	-16	6	-36
Pitavastatin 4 mg daily	319	-44	-35	-32	-17	6	-41
Simvastatin 10 mg daily	107	-35	-27	-25	-16	6	-32
Simvastatin 20 mg daily	110	-43	-34	-31	-16	7	-39
Simvastatin 80 mg daily	--Not Studied-----------------------------------						

Active-controlled study with pravastatin in elderly (NK-104-306)

Pitavastatin was compared with the HMG-CoA reductase inhibitor pravastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled non-inferiority Phase 3 study of 942 elderly patients (≥ 65 years) with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6 to 8 week wash-out/dietary lead-in period, and then were randomized to a once daily dose of pitavastatin or pravastatin for 12 weeks (Table 7). Non-inferiority of pitavastatin to a given dose of pravastatin was assumed if the lower bound of the 95% CI for the treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 7. Pitavastatin significantly reduced LDL-C compared to pravastatin as demonstrated by the following pairwise dose comparisons: pitavastatin 1 mg vs. pravastatin 10 mg, pitavastatin 2 mg vs. pravastatin 20 mg and pitavastatin 4 mg vs. pravastatin 40 mg. Mean treatment differences (95% CI) were 9% (6%, 12%), 10% (7%, 13%) and 10% (7%, 13%), respectively.

Table 7 Response by Dose of Pitavastatin and Pravastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
Pitavastatin 1 mg daily	207	-31	-25	-22	-13	1	-29
Pitavastatin 2 mg daily	224	-39	-31	-27	-15	2	-36
Pitavastatin 4 mg daily	210	-44	-37	-31	-22	4	-41
Pravastatin 10 mg daily	103	-22	-17	-15	-5	0	-20
Pravastatin 20 mg daily	96	-29	-22	-21	-11	-1	-27
Pravastatin 40 mg daily	102	-34	-28	-24	-15	1	-32
Pravastatin 80 mg daily	-------------------------------------Not Studied-------------------------------						

Active-controlled study with simvastatin in patients with ≥ 2 risk factors for coronary heart disease (NK-104-304)

Pitavastatin was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 351 patients with primary hyperlipidemia or mixed dyslipidemia with ≥ 2 risk factors for coronary heart disease. After a 6 to 8 week wash-out/dietary lead-in period, patients were randomized to a 12 week treatment with either pitavastatin or simvastatin (Table 8). Non-inferiority of pitavastatin to simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 8. Pitavastatin 4 mg was non-inferior to simvastatin 40 mg for percent change from baseline to endpoint in LDL-C. The mean treatment difference (95% CI) was 0% (-2%, 3%).

Table 8 Response by Dose of Pitavastatin and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia with ≥ 2 Risk Factors for Coronary Heart Disease (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
Pitavastatin 4 mg daily	233	-44	-34	-31	-20	7	-40
Simvastatin 40 mg daily	118	-44	-34	-31	-15	5	-39
Simvastatin 80 mg daily	--Not Studied--------------------------------						

Active-controlled study with atorvastatin in patients with type II diabetes mellitus (NK-104-305)
Pitavastatin was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, non-inferiority Phase 3 study of 410 subjects with type II diabetes mellitus and combined dyslipidemia. Patients entered a 6 to 8 week washout/dietary lead-in period and were randomized to a once daily dose of pitavastatin or atorvastatin for 12 weeks. Non-inferiority of pitavastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

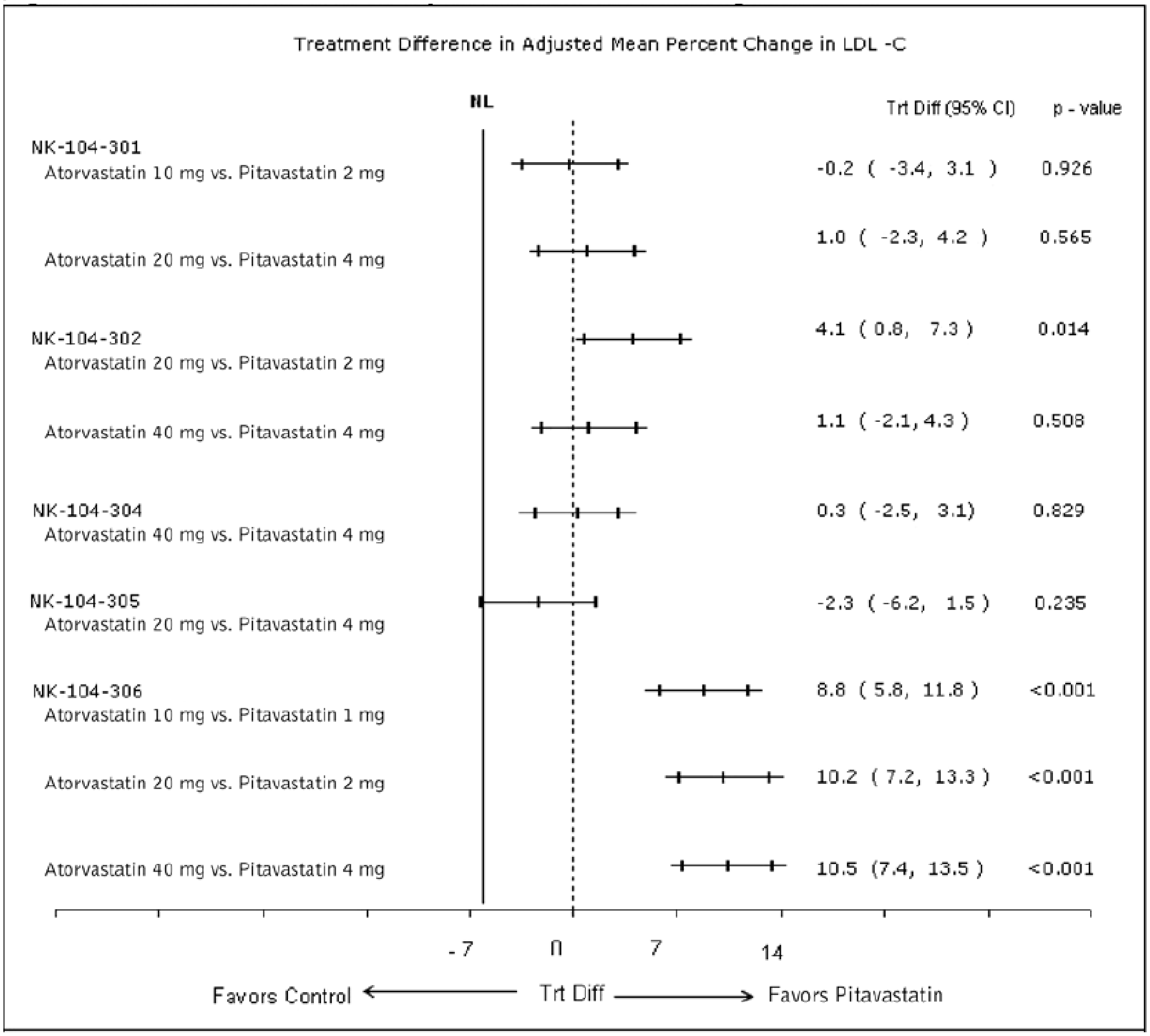
Lipid results are shown in Table 9. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit so that the non-inferiority objective was not achieved.

Table 9 Response by Dose of Pitavastatin and Atorvastatin in Patients with Type II Diabetes Mellitus and Combined Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
Pitavastatin 4 mg daily	274	-41	-32	-28	-20	7	-36
Atorvastatin 20 mg daily	136	-43	-34	-32	-27	8	-40
Atorvastatin 40 mg daily	-----------------------------------Not Studied---						
Atorvastatin 80 mg daily	-----------------------------------Not Studied---						

The treatment differences in efficacy in LDL-C change from baseline between Pitavastatin and active controls in the Phase 3 studies are summarized in Figure 1.

Figure 1 Treatment Difference in Adjusted Mean Percent Change in LDL-C



NL=non-inferiority limit.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYPITAMAG (pitavastatin) Tablets, 1 mg are white to off-white, beveled-edge, round-shaped tablets debossed with “876” on one side and plain on the other side and are supplied as follows:

NDC 68382-876-06 in bottle of 30 tablets
NDC 68382-876-16 in bottle of 90 tablets
NDC 68382-876-01 in bottle of 100 tablets
NDC 68382-876-05 in bottle of 500 tablets
NDC 68382-876-10 in bottle of 1000 tablets
NDC 68382-876-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

ZYPITAMAG (pitavastatin) Tablets, 2 mg are white to off-white, beveled-edge, round-shaped tablets debossed with “877” on one side and plain on the other side and are supplied as follows:

NDC 68382-877-06 in bottle of 30 tablets
NDC 68382-877-16 in bottle of 90 tablets
NDC 68382-877-01 in bottle of 100 tablets

NDC 68382-877-05 in bottle of 500 tablets
NDC 68382-877-10 in bottle of 1000 tablets
NDC 68382-877-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

ZYPITAMAG (pitavastatin) Tablets, 4 mg are white to off-white, beveled-edge, round-shaped tablets debossed with “878” on one side and plain on the other side and are supplied as follows:

NDC 68382-878-06 in bottle of 30 tablets
NDC 68382-878-16 in bottle of 90 tablets
NDC 68382-878-01 in bottle of 100 tablets
NDC 68382-878-05 in bottle of 500 tablets
NDC 68382-878-10 in bottle of 1000 tablets
NDC 68382-878-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

Storage
Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].
Protect from moisture and light.

17 PATIENT COUNSELING INFORMATION

The patient should be informed of the following:

Dosing Time
ZYPITAMAG can be taken at any time of the day with or without food.

Muscle Pain
Patients should be advised to promptly notify their physician of any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever, or if these muscle signs or symptoms persist after discontinuing ZYPITAMAG. They should discuss all medication, both prescription and over the counter, with their physician.

Embryo-fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and to inform their healthcare professional of a known or suspected pregnancy *[see Contraindications (4), Use in Specific Populations (8.1, 8.3)]*.

Lactation
Advise women not to breastfeed during treatment with ZYPITAMAG *[see Contraindications (4), Use in Specific Populations (8.2)]*.

Liver Enzymes
It is recommended that liver enzyme tests be checked before the initiation of ZYPITAMAG and if signs or symptoms of liver injury occur. All patients treated with ZYPITAMAG should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

Please address medical inquiries to (MedicalAffairs@zydususa.com) Tel.: 1-877-993-8779.

This product’s label may have been updated. For current full prescribing information, please visit www.zydususa.com

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