ZYPITAMAG- pitavastatin magnesium tablet, film coated
Medicure International Inc

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

RECENT MAJOR CHANGES

Warnings and Precautions, IMNM (5.2) 6/2020

INDICATIONS AND USAGE

ZYPITAMAG is an HMG-CoA reductase inhibitor indicated as an adjunctive therapy to diet in adult patients with primary hyperlipidemia or mixed dyslipidemia 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)

Limitations of Use:
The effect of ZYPITAMAG on cardiovascular morbidity and mortality has not been determined. (1)

DOSAGE AND ADMINISTRATION

- Take ZYPITAMAG orally once daily with or without food at the same time each day (2.1)
- Individualize the dose of ZYPITAMAG according to patient characteristics, goal of therapy, and response (2.1).
- After initiation or upon titration, analyze lipid levels after 4 weeks and adjust the dosage accordingly (2.1).
- The recommended starting ZYPITAMAG dosage is 2 mg once daily (2.2).
- The maximum recommended dosage is ZYPITAMAG 4 mg once daily (2.2).
- The recommended starting dosage for patients with moderate and severe renal impairment (estimated glomerular filtration rate 30-59 and 15-29 mL/min/1.73 m^2, respectively) as well as end-stage renal disease on hemodialysis is pitavastatin 1 mg once daily and the maximum dose is 2 mg once daily. ZYPITAMAG is not available in a 1 mg dose; use an alternative formulation of pitavastatin (2.3).
- There are ZYPITAMAG dosage adjustments due to drug interactions for:
  - Patients taking erythromycin, do not exceed 1 mg once daily. ZYPITAMAG is not available in a 1 mg dose; use an alternative formulation of pitavastatin (2.4).
  - Patients taking rifampin, do not exceed 2 mg once daily (2.4).

DOSAGE FORMS AND STRENGTHS

- Tablets: 2 mg and 4 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to product components (4, 6.1)
- Coadministration with cyclosporine (4, 7)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4, 5.3)
- Pregnancy (4, 8.1, 8.3)
- Lactation (4, 8.2)

WARNINGS AND PRECAUTIONS

- *Myopathy and Rhabdomyolysis:* Risk factors include age 65 and greater, renal impairment, inadequately treated hypothyroidism, and higher doses of ZYPITAMAG. Discontinue ZYPITAMAG if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue ZYPITAMAG in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis, e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the ZYPITAMAG dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever (5.1).

- *Immune-Mediated Necrotizing Myopathy (IMNM):* There have been rare reports of 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; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents (5.2).
- *Hepatic Dysfunction:* Increases in serum transaminases can occur. Rare postmarketing reports of fatal and non-fatal hepatic failure have occurred. Consider liver enzyme testing before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue ZYPITAMAG (5.3)
- *Increases in HbA1c and Fasting Serum Glucose Levels:* Have been reported with statins, including ZYPITAMAG. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices. (5.4)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Medicure at 1-800-509-0544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- *Gemfibrozil:* Avoid concomitant use with ZYPITAMAG (7)
- *Fibrates:* Consider if the benefit of using fibrates concomitantly with ZYPITAMAG outweighs the increased risk of myopathy and rhabdomyolysis (7)
- *Niacin:* Consider if the benefit of using lipid-modifying doses (>1 g/day) of niacin concomitantly with ZYPITAMAG outweighs the increased risk of myopathy and rhabdomyolysis (7)
- *Colchicine:* Consider the risk/benefit of concomitant use with ZYPITAMAG (7)

USE IN SPECIFIC POPULATIONS

- *Females of Reproductive Potential:* Advise females to use effective contraception during treatment. (8.3)

Pediatric use information is approved for Kowa Co Ltd's LIVALO (pitavastatin) tablets. However, due to Kowa Co Ltd's marketing exclusivity rights, this drug product is not labeled with that information

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYPITAMAG is indicated as an adjunctive therapy to diet in adult patients with primary hyperlipidemia or mixed dyslipidemia 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).

Limitations of Use

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

Pediatric use information is approved for Kowa Co Ltd's LIVALO (pitavastatin) tablets. However, due to Kowa Co Ltd's marketing exclusivity rights, this drug product is not labeled with that information.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage and Administration Information

- Take ZYPITAMAG orally once daily with or without food at the same time each day.
- Individualize the dose of ZYPITAMAG according to patient characteristics, goal of

therapy, and response.
- After initiation or upon titration of ZYPITAMAG, analyze lipid levels after 4 weeks and adjust the dosage accordingly.

2.2 Recommended Dosage for Adults
- The recommended starting ZYPITAMAG dosage is 2 mg once daily.
- The maximum recommended dosage is ZYPITAMAG 4 mg once daily *[see Warnings and Precautions (5.1)]*.

2.3 Recommended Dosage in Patients with Renal Impairment
- The recommended starting dose for patients with moderate and severe renal impairment (estimated glomerular filtration rate 30 – 59 mL/minute/1.73 m^2 and 15 – 29 mL/minute/1.73 m^2, respectively) and patients with end-stage renal disease receiving hemodialysis is pitavastatin 1 mg once daily. ZYPITAMAG is not available in a 1 mg dose; use an alternative formulation of pitavastatin for the 1 mg dose.
- The maximum recommended dose for these patients is ZYPITAMAG 2 mg once daily *[see Use in Specific Populations (8.6)]*.

2.4 ZYPITAMAG Dosage Adjustments Due to Drug Interactions
- In patients taking erythromycin, do not exceed pitavastatin 1 mg once daily *[see Drug Interactions (7)]*. ZYPITAMAG is not available in a 1 mg dose; use an alternative formulation of pitavastatin for the 1 mg dose.
- In patients taking rifampin, do not exceed ZYPITAMAG 2 mg once daily *[see Drug Interactions (7)]*.

Pediatric use information is approved for Kowa Co Ltd's LIVALO (pitavastatin) tablets. However, due to Kowa Co Ltd's marketing exclusivity rights, this drug product is not labeled with that information

3 DOSAGE FORMS AND STRENGTHS
- 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
ZYPITAMAG is contraindicated in the following conditions:
- Known hypersensitivity to pitavastatin or any inactive ingredient in ZYPITAMAG. Hypersensitivity reactions including angioedema, rash, pruritus, and urticaria have been reported with pitavastatin *[see Adverse Reactions (6.1)]*.
- Concomitant use of cyclosporine *[see Drug Interactions (7)]*.
- Active liver disease including unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions (5.3)]*.
- Pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.
- Lactation. It is not known if pitavastatin 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, females who require

pitavastatin treatment should not breastfeed their infants *[see Use in Specific Populations (8.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

ZYPITAMAG may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Rare fatalities have occurred as a result of rhabdomyolysis with statin use, including pitavastatin.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use of certain drugs, and higher ZYPITAMAG dosage. Dosages of pitavastatin greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. The maximum recommended dose of ZYPITAMAG is 4 mg once daily *[see Dosage and Administration (2.2)]*.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

ZYPITAMAG is contraindicated in patients taking cyclosporine and not recommended in patients taking gemfibrozil *[see Contraindications (4) and Drug Interactions (7)]*. There are ZYPITAMAG dosage restrictions for patients taking erythromycin or rifampin *[see Dosage and Administration (2.4)]*. The following drugs when used concomitantly with ZYPITAMAG may also increase the risk of myopathy and rhabdomyolysis: lipid-modifying dosages of niacin (>1 grams/day), fibrates, and colchicine *[see Drug Interactions (7)]*.

Discontinue ZYPITAMAG if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if ZYPITAMAG is discontinued. Temporarily discontinue ZYPITAMAG in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis, e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the ZYPITAMAG dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

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; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with ZYPITAMAG *[see Adverse Reactions (6)]*. In most cases, the elevations were transient and either resolved or improved on continued therapy or after a brief interruption in therapy. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.

Consider liver enzyme testing before the initiation of ZYPITAMAG and thereafter, when clinically indicated. ZYPITAMAG is contraindicated in patients with active liver disease including unexplained persistent elevations in hepatic transaminase levels *[see Contraindications (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue ZYPITAMAG.

5.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including pitavastatin. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in other sections of the labeling:

- Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)].*
- Immune-Mediated Necrotizing Myopathy *[see Warnings and Precautions (5.2)]*
- Hepatic Dysfunction *[see Warnings and Precautions (5.3)]*
- Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of one drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults with Primary Hyperlipidemia and Mixed Dyslipidemia

In 10 controlled clinical studies and 4 subsequent open-label extension studies, 3,291 adult patients with primary hyperlipidemia or mixed dyslipidemia 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 – 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.

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).

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 (≥ 2% and ≥ placebo) in Adult Patients with Primary Hyperlipidemia and Mixed Dyslipidemia in Studies up to 12 Weeks

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

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

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

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

Adverse Reactions in Adult HIV-Infected Patients with Dyslipidemia

In a double-blind, randomized, controlled, 52-week trial, 252 HIV-infected patients with dyslipidemia were treated with either pitavastatin 4 mg 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 (ULN), which resolved spontaneously. Four patients (3%) treated with pitavastatin had at least one ALT value exceeding 3 times but less than 5 times the 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.

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6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

Gastrointestinal disorders: abdominal discomfort, abdominal pain, dyspepsia, nausea

General disorders: asthenia, fatigue, malaise, dizziness

Hepatobiliary disorders: hepatitis, jaundice, fatal and non-fatal hepatic failure

Immune system disorders: angioedema, immune-mediated necrotizing myopathy associated with statin use

Metabolism and nutrition disorders: increases in HbA1c, fasting serum glucose levels

Musculoskeletal and connective tissue disorders: muscle spasms, myopathy, rhabdomyolysis

Nervous system disorders: hypoesthesia, peripheral neuropathy

Psychiatric disorders: insomnia, depression. Rare reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. Cognitive impairment was generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: interstitial lung disease

7 DRUG INTERACTIONS

Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with ZYPITAMAG

Table 2 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when
administered concomitantly with ZYPITAMAG and instructions for preventing or managing drug
interactions *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

Table 2. Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with ZYPITAMAG

Cyclosporine	
Clinical Impact:	Cyclosporine significantly increases pitavastatin exposure and increases the risk of myopathy and rhabdomyolysis.
Intervention:	Concomitant use of cyclosporine with ZYPITAMAG is contraindicated *[see Contraindications (4)].*
Gemfibrozil	
Clinical Impact:	Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of gemfibrozil with statins, including pitavastatin.
Intervention:	Avoid concomitant use of gemfibrozil with ZYPITAMAG.
Erythromycin	
Clinical Impact:	Erythromycin significantly increases pitavastatin exposure and increases the risk of myopathy and rhabdomyolysis.

Intervention:	In patients taking erythromycin, do not exceed ZYPITAMAG 1 mg once daily *[see Dosage and Administration (2.4)].*
Rifampin	
Clinical Impact:	Rifampin significantly increases peak pitavastatin exposure and increases the risk of myopathy and rhabdomyolysis.
Intervention:	In patients taking rifampin, do not exceed ZYPITAMAG 2 mg once daily *[see Dosage and Administration (2.4)].*
Fibrates	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with statins, including pitavastatin.
Intervention:	Consider if the benefit of using fibrates concomitantly with ZYPITAMAG outweighs the increased risk of myopathy and rhabdomyolysis.
Niacin	
Clinical Impact:	The risk of myopathy and rhabdomyolysis may be increased with concomitant use of lipid-modifying doses (1 g/day) of niacin with pitavastatin.
Intervention:	Consider if the benefit of using lipid-modifying doses (>1 g/day) of niacin concomitantly with ZYPITAMAG outweighs the increased risk of myopathy and rhabdomyolysis.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with statins, including pitavastatin.
Intervention:	Consider the risk/benefit of concomitant use of colchicine with ZYPITAMAG.

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)]*. There is no available information on 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

The safety and effectiveness of ZYPITAMAG have not been established in pediatric patients younger than 8 years of age with heterozygous familial hypercholesterolemia (HeFH) or in pediatric patients with other types of hyperlipidemia (other than HeFH).

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8.5 Geriatric Use

In controlled clinical studies, 1,209 (43%) patients were 65 years and older. No significant differences in efficacy or safety were observed between geriatric patients and younger patients. Advanced age (≥ 65 years) is a risk factor for myopathy and rhabdomyolysis. In general, dose selection for a geriatric patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Due to the risk of myopathy, a dosage modification of ZYPITAMAG is recommended for patients with moderate and severe renal impairment (estimated glomerular filtration rate 30 – 59 mL/min/1.73 m^2 and 15 – 29 mL/min/1.73 m^2, respectively), as well as end-stage renal disease receiving hemodialysis *[see Dosage and Administration (2.3), Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

ZYPITAMAG is contraindicated in patients with active liver disease including unexplained persistent elevations of hepatic transaminase levels *[see Contraindications (4), Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

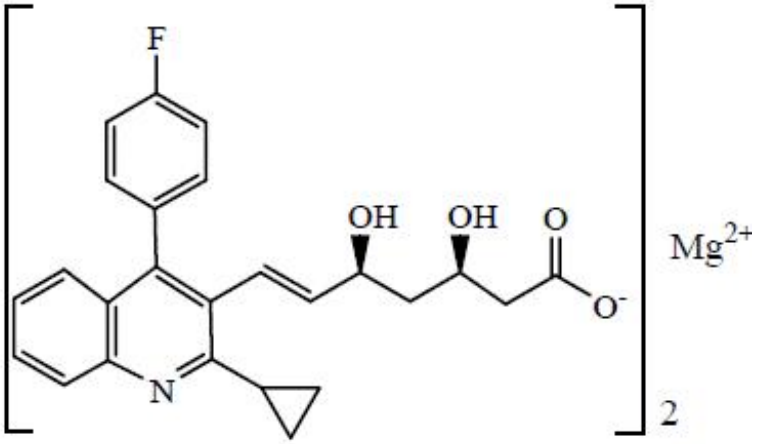
No specific treatment for pitavastatin overdose is known. Contact Poison Control (1-800-222-1222) for latest recommendations. Hemodialysis is unlikely to be of benefit due to high protein binding ratio of pitavastatin.

11 DESCRIPTION

ZYPITAMAG (pitavastatin) tablets for oral use is an HMG-CoA reductase inhibitor.

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 2.053 mg or 4.106 mg of pitavastatin magnesium, which is equivalent to 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 is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, a rate-limiting step in the biosynthetic pathway for cholesterol. 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. Sustained inhibition of cholesterol synthesis in the liver also decreases levels of very low density lipoproteins.

12.2 Pharmacodynamics

Cardiac Electrophysiology
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 dose of 4 mg daily).

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%. 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.

Effect of Food
Administration of pitavastatin with a high fat meal (50% fat content) decreases pitavastatin C_{max} by 43% but does not significantly reduce pitavastatin AUC.

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.

Elimination
Metabolism
The principal route of pitavastatin metabolism is glucuronidation via liver uridine 5'-diphosphate glucuronosyltransferase (UGT) with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system. 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 UGTs (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.

Specific Populations
Racial or Ethnic Groups
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.

Male and Female Patients
In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C_{max} and AUC were 60 and 54% higher, respectively in females.

Geriatric Patients
In a pharmacokinetic study which compared healthy young and geriatric (≥ 65 years) volunteers, pitavastatin C_{max} and AUC were 10 and 30% higher, respectively, in the geriatric patients *[see Use in Specific Populations (8.5)]*

Pediatric Patients
Pediatric use information is approved for Kowa Co Ltd's LIVALO (pitavastatin) tablets.

However, due to Kowa Co Ltd's marketing exclusivity rights, this drug product is not labeled with that information.

Patients with Renal Impairment

In patients with moderate renal impairment (estimated 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 *[see Use in Specific Populations (8.6)]*.

In another pharmacokinetic study, patients with severe renal impairment (estimated 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% *[see Use in Specific Populations (8.6)]*.

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

Patients with Hepatic Impairment
The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. Pitavastatin C_{max} and AUC_{inf} in patients with moderate hepatic impairment (Child-Pugh B disease) was 2.7-fold and 3.8-fold higher, respectively as compared to health volunteers. In patients with mild hepatic impairment (Child-Pugh A disease), pitavastatin C_{max} and AUC_{inf} were 30% and 60% higher as compared to healthy volunteers. Mean pitavastatin half-life for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively *[see Contraindications (4), Warnings and Precautions (5.3)]*.

Drug Interaction Studies

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.

Table 3 presents the effect of coadministered drugs on pitavastatin systemic exposure:

Table 3 Effect of Coadministered Drugs on Pitavastatin Systemic Exposure

Coadministered drug	Dosage 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 †
	Pitavastatin 4 mg QD + rifampin 600 mg		

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%
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 4 presents the effect of pitavastatin coadministration on systemic exposure of other drugs:

Table 4 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%
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 daily, 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 daily 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 daily 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 daily 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

Central Nervous System (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 in Adult Patients

Active-Controlled Study with Atorvastatin (Study 301)

Pitavastatin was compared with Atorvastatin Calcium Tablets (referred to as atorvastatin) in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority study of 817 adult 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 Lipid Response by Dose of Pitavastatin and Atorvastatin in Adult Patients with Primary Hyperlipidemia or Mixed Dyslipidemia in Study 301 (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

Active-Controlled Study with Simvastatin (Study 302)

Pitavastatin was compared with Simvastatin Tablets (referred to as simvastatin) in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority study of 843 adult 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 Lipid Response by Dose of Pitavastatin and Simvastatin in Adult Patients with Primary Hyperlipidemia or Mixed Dyslipidemia in Study 302 (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 20 mg daily	107	-35	-27	-25	-16	6	-32
Simvastatin 40 mg daily	110	-43	-34	-31	-16	7	-39

Active-Controlled Study with Pravastatin in Geriatric Patients (Study 306)

Pitavastatin was compared with Pravastatin Sodium Tablets (referred to as pravastatin) in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled non-inferiority study of 942 geriatric 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 Lipid Response by Dose of Pitavastatin and Pravastatin in Geriatric Patients with Primary Hyperlipidemia or Mixed Dyslipidemia in Study 306 (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

Active-Controlled Study with Simvastatin in Patients with ≥ 2 Risk Factors for Coronary Heart Disease (Study 304)

Pitavastatin was compared with Simvastatin Tablets (referred to as simvastatin) in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority study of 351 adult 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 Lipid Response by Dose of Pitavastatin and Simvastatin in Adult Patients with Primary Hyperlipidemia or Mixed Dyslipidemia with ≥ 2 Risk Factors for Coronary Heart Disease in Study 304 (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

Active- Controlled Study with Atorvastatin in Patients with Type 2 Diabetes Mellitus (Study 305)

Pitavastatin was compared with Atorvastatin Calcium Tablets (referred to as atorvastatin) in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, non-inferiority study of 410 adult patients with type 2 diabetes mellitus and mixed dyslipidemia. Patients entered a 6 to 8 week wash-out/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.

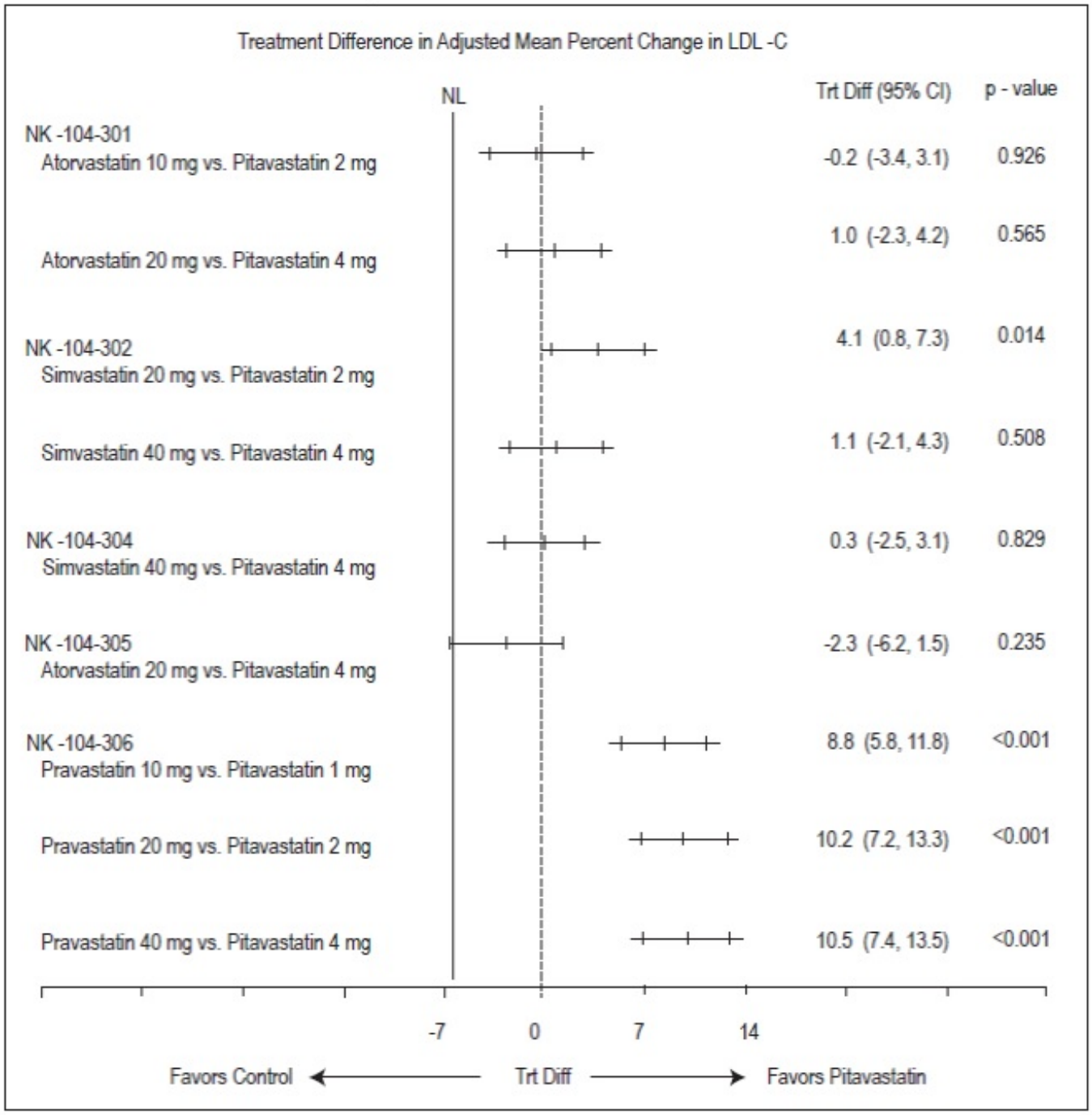
Lipid results are shown in Table 9. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit The study failed to demonstrate that pitavastatin was not significantly different than atorvastatin in lowering LDL-C in patients with type 2 diabetes mellitus and mixed dyslipidemia.

Table 9 Lipid Response by Dose of Pitavastatin and Atorvastatin in Patients with Type 2 Diabetes Mellitus and Mixed Dyslipidemia in Study 305 (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

The treatment differences in efficacy in LDL-C change from baseline between pitavastatin and active controls (i.e., atorvastatin, simvastatin, or pravastatin) in the in the active-controlled studies described above are summarized in Figure 1.

Figure 1 Treatment Difference in Adjusted Mean Percent Change in LDL-C between Pitavastatin and the Comparator (Atorvastatin, Simvastatin, or Pravastatin)



NL=non-inferiority limit.

Pediatric use information is approved for Kowa Co Ltd's LIVALO (pitavastatin) tablets. However, due to Kowa Co Ltd's marketing exclusivity rights, this drug product is not labeled with that information.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 25208-201-13 in bottle of 30 tablets with child-resistant closure

NDC 25208-201-09 in bottle of 90 tablets with child-resistant closure
NDC 25208-201-14 in bottle of 100 tablets
NDC 25208-201-15 in bottle of 500 tablets
NDC 25208-201-11 in bottle of 1000 tablets
NDC 25208-201-12 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 25208-202-13 in bottle of 30 tablets with child-resistant closure
NDC 25208-202-09 in bottle of 90 tablets with child-resistant closure
NDC 25208-202-14 in bottle of 100 tablets
NDC 25208-202-15 in bottle of 500 tablets
NDC 25208-202-11 in bottle of 1000 tablets
NDC 25208-202-12 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:

Myopathy and Rhabdomyolysis
Advise patients that ZYPITAMAG may cause myopathy and rhabdomyolysis. Inform patients that the risk is increased when taking certain types of medication and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.1)]*.

Hepatic Dysfunction
Inform patients that ZYPITAMAG may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice *[see Warnings and Precautions (5.3)]*.

Increases in HbA1c and Fasting Serum Glucose Levels
Inform patients that increases in HbA1c and fasting serum glucose levels may occur with ZYPITAMAG. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.4)]*.

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 (medical.information@medicure.com) Tel.: 1-800-509-0544.
This product's label may have been updated. For current full prescribing information, please visit www. medicure.com

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Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India
Distributed by:
Medicure
Princeton, NJ 08540 USA

Rev.: 09/2020
PIM-ZYP-06

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 25208-201-09

Zypitamag (Pitavastatin) Tablets, 2 mg

90 Tablets

Rx only

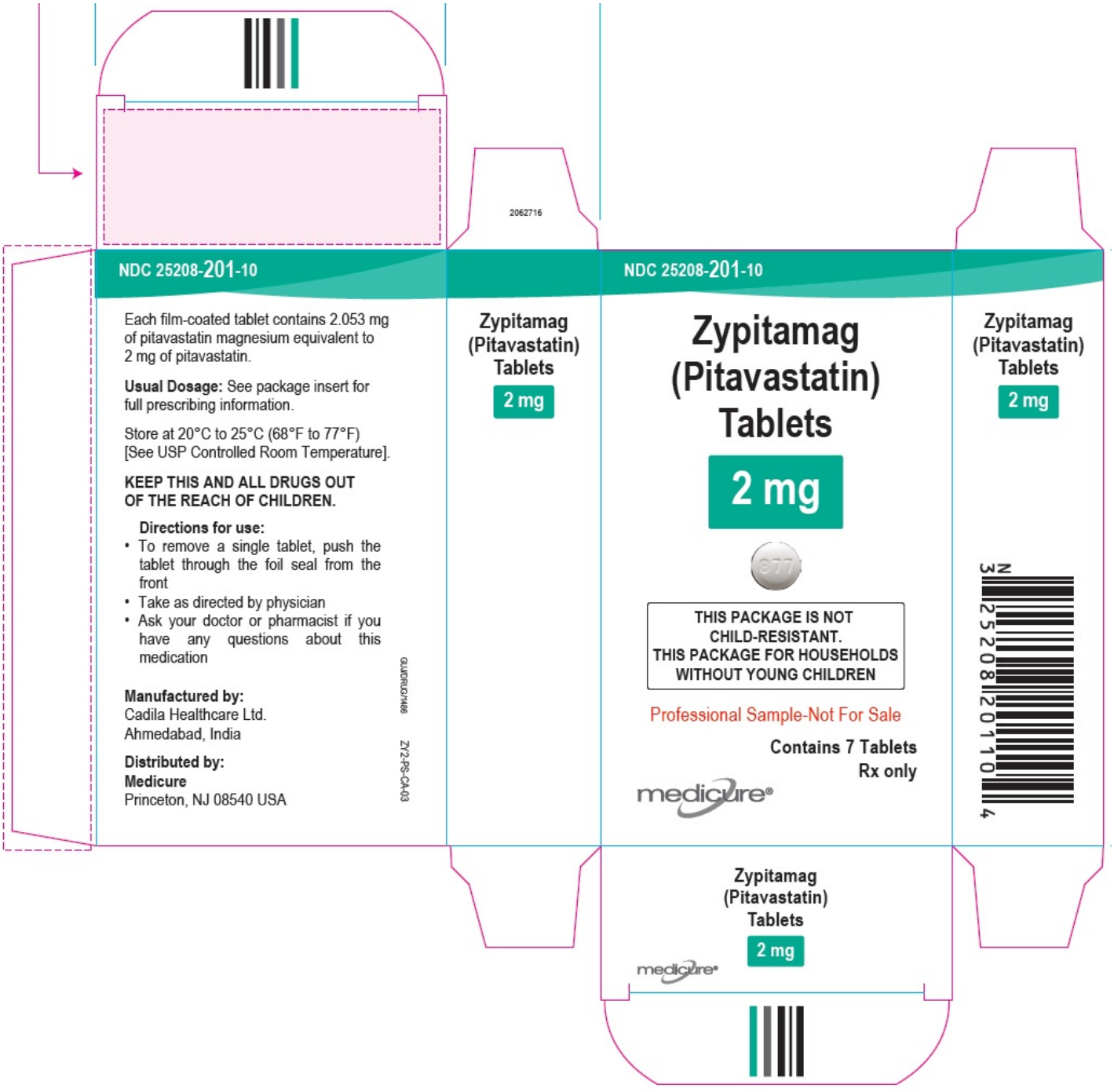
NDC 25208-201-10

Zypitamag (Pitavastatin) Tablets, 2 mg

7 Tablets Blister Carton

Rx only

Professional Sample-Not For Sale

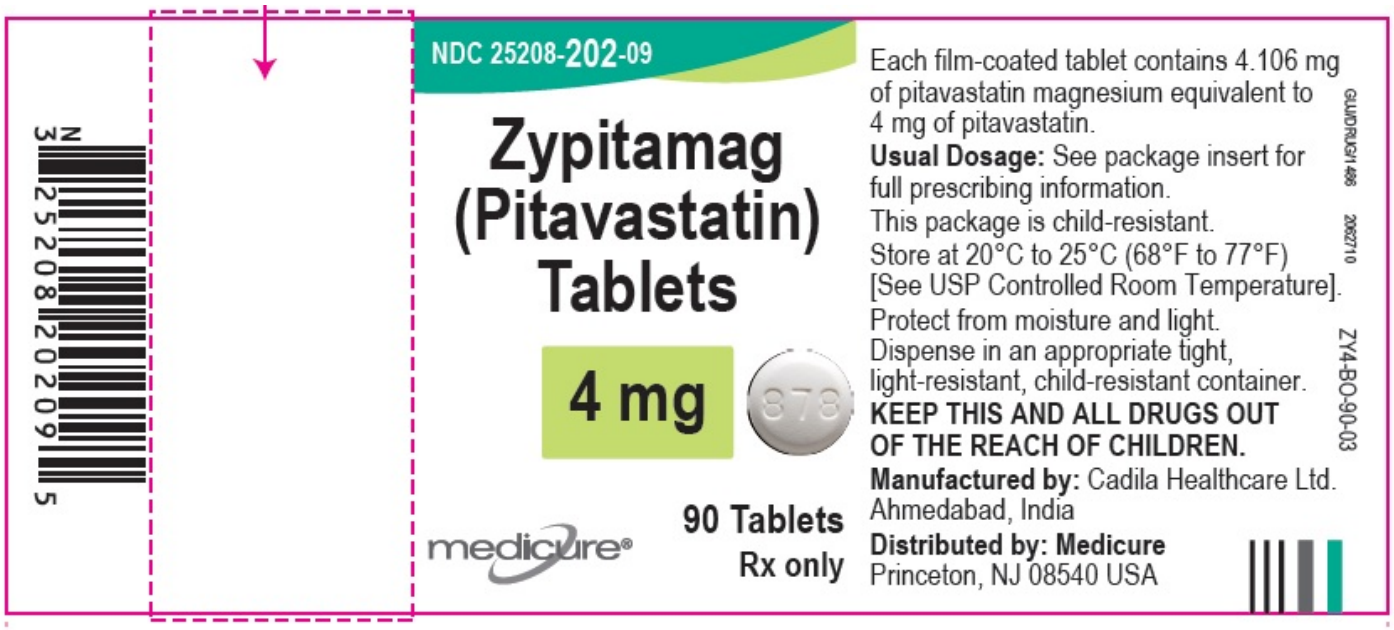


NDC 25208-202-09

Zypitamag (Pitavastatin) Tablets, 4 mg

90 Tablets

Rx only



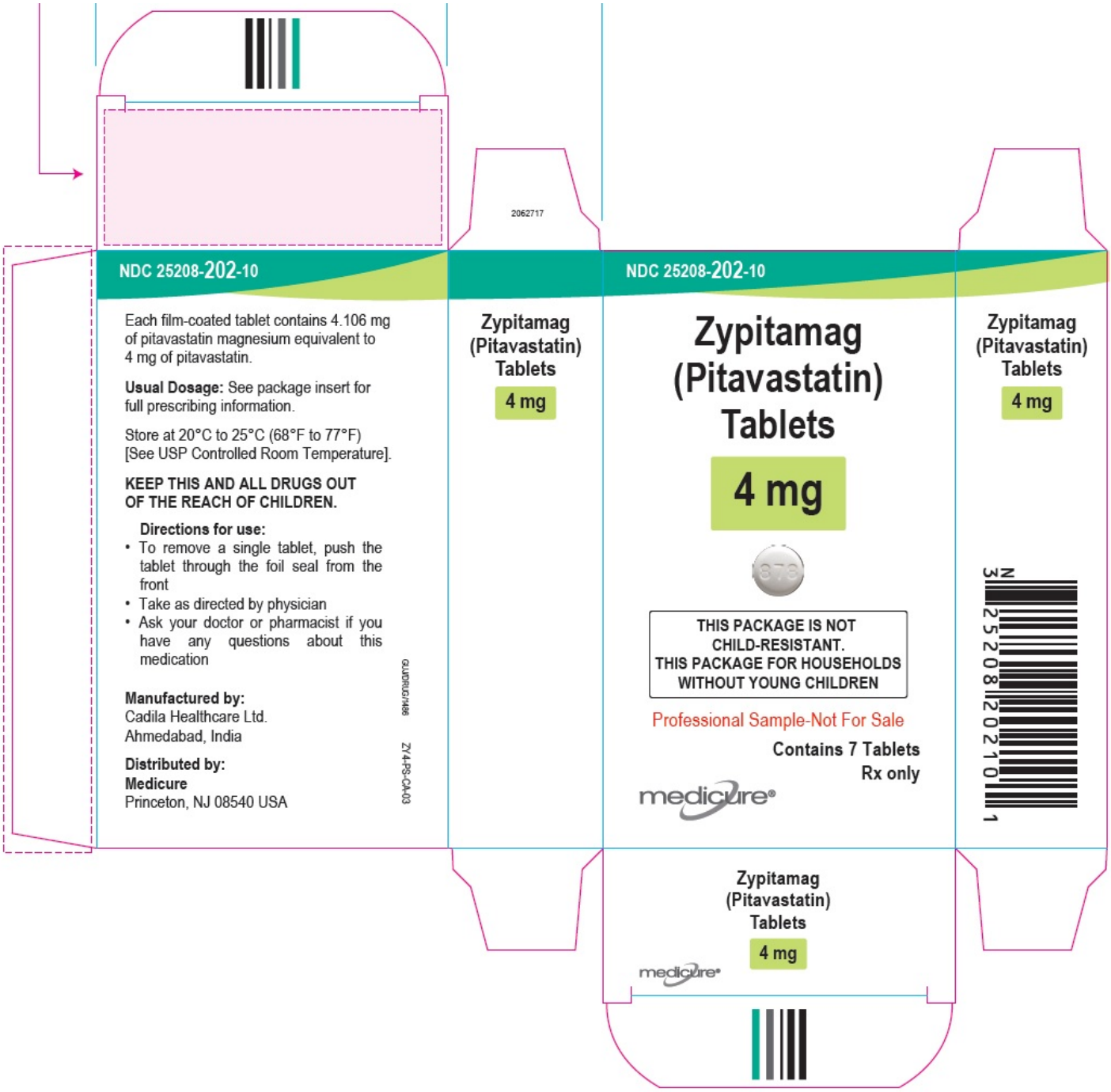
NDC 25208-202-10

Zypitamag (Pitavastatin) Tablets, 4 mg

7 Tablets Blister Carton

Rx only

Professional Sample-Not For Sale



ZYPITAMAG

pitavastatin magnesium tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:25208-201
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PITAVASTATIN (UNII: M5681Q5F9P) (PITAVASTATIN - UNII:M5681Q5F9P)	PITAVASTATIN	2 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM CARBONATE (UNII: H0G9379FGK)	
CROSPOVIDONE (UNII: 2S7830E561)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white (off white)	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	877
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:25208-201-13	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
2	NDC:25208-201-09	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
3	NDC:25208-201-14	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
4	NDC:25208-201-15	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
5	NDC:25208-201-11	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
6	NDC:25208-201-12	10 in 1 CARTON	03/09/2018	
6		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
7	NDC:25208-201-10	1 in 1 CARTON	03/09/2018	
7		7 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208379	03/09/2018	

ZYPITAMAG

pitavastatin magnesium tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:25208-202
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PITAVASTATIN (UNII: M5681Q5F9P) (PITAVASTATIN - UNII:M5681Q5F9P)	PITAVASTATIN	4 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM CARBONATE (UNII: H0G9379FGK)	
CROSPOVIDONE (UNII: 2S7830E561)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	white (off white)	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	878
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:25208-202-13	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
2	NDC:25208-202-09	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
3	NDC:25208-202-14	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
4	NDC:25208-202-15	500 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
5	NDC:25208-202-11	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/09/2018	
6	NDC:25208-202-12	10 in 1 CARTON	03/09/2018	
6		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

7	NDC:25208-202-10	1 in 1 CARTON	03/09/2018	
7		7 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208379	03/09/2018	

Labeler - Medicure International Inc (860240324)

Registrant - Zydus Pharmaceuticals (USA) Inc. (156861945)

Establishment

Name	Address	ID/FEI	Business Operations
Cadila Healthcare Limited		918596198	analysis(25208-201, 25208-202) , manufacture(25208-201, 25208-202)

Revised: 12/2022 Medicure International Inc