1.5.1

Prescribing Information (Summary of Product Characteristics)

1.5.1.1 Name of the medicinal Product

Atorvastatin Tablets 20 mg

1.5.1.2 Qualitative and Quantitative Composition

1.5.1.2.1 Qualitative declaration

Atorvastatin Calcium

1.5.1.2.2 Quantitative declaration

Sr. No.	Ingredients Chemical Name	Specification	Standard Quantity (mg/Tablet)	Reason for Inclusion
01	Atorvastatin Calcium Eq. to Atorvastatin	IHS	20.70 Eq. to 20.00	HMG-CoA Reductase Inhibitor
02	Calcium Carbonate	BP	72.000	Buffering agent
03	Lactose Monohydrate	BP	131.30	Diluent
04	Microcrystalline Cellulose (pH 102)	BP	60.00	Diluent
05	Povidone (P.V.P.K.-30)	BP	6.000	Binding Agent
06	Polysorbate-80 (Tween-80)	BP	0.800	Solubilizing Agent
08	Croscarmellose Sodium	USP-NF	8.000	Disintegrating Agent
09	Magnesium Stearate	BP	1.200	Lubricant
10	Opadry White YS-1-7040	IHS	8.000	Colourant
11	Polysorbate-80 (Tween-80)	BP	1.600	Solubilizing Agent
12	Simethicone 30%	USP	0.400	Antifoaming Agent
13	Purified Water	BP	Q.S	Vehicle

1.5.1.3 Pharmaceutical Form

Oral Tablet

White to off-white coloured, round shaped, biconvex, film coated tablet, break line on one side and plain on other side.

1.5.1.4 Clinical Particulars

1.5.1.4.1 Therapeutic Indications

Primary Hypercholesterolemia, heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia or combined (mixed) hyperlipidemia in patients who have not responded adequately to diet and other appropriate measures.

Prevention of cardiovascular events in patients at high risk of a first cardiovascular event.

1.5.1.4.2 Posology and Method of Administration

Dosage:

Adults:

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia:

Initially: 10 or 20 mg daily may increase at 4-week intervals. May initiate with 40 mg once daily in patients who require >45% reduction in low-density lipoprotein cholesterol.

Maximum dose: 80 mg/day.

Heterozygous familial hypercholesterolaemia:

Inital: 10 or 20 mg once daily, may increase slowly if needed.

Maximum: 80 mg/day.

Prevention of cardiovascular disease:

Initial: 10 mg daily. Higher doses may be necessary in order to attain (LDL-) cholesterol levels or as directed by physician.

Pediatric use:

Hypercholesterolaemia:

10 mg once daily; maximum recommended dose: 20 mg once daily.

Hepatic impairment:

Atorvastatin should be used with caution in patients with hepatic impairment.

Method of Administration: Oral

1.5.1.4.3 Contraindications

Atorvastatin is contraindicated in:

Patients with hypersensitivity to the active substance or to any of the excipients of this medicinal product.

Patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.

Patients with myopathy.

During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

1.5.1.4.4 Special Warnings and Special Precautions for Use

Patients with history of liver disease or high alcohol intake.

Patients with risk factor of myopathy or rhabdomyolysis.

Pregnancy & Lactation :

Atorvastatin should be avoiding use in pregnancy and in mothers who are breast-feeding.

1.5.1.4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 3A4 inhibitors: Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided.

CYP3A4 inducers: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin.

Transport protein inhibitors: Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin. If concomitant administration, a dose reduction and clinical monitoring for efficacy is recommended.

Gemfibrozil / fibric acid derivatives: The risk of muscle related events, including rhabdomyolysis may be increased with the concomitant use of fibric acid derivatives and atorvastatin.

Ezetimibe: The risk of muscle related events, including rhabdomyolysis may be increased with concomitant use of ezetimibe and atorvastatin.

Colestipol: When colestipol was co-administered with Atorvastatin plasma concentrations of atorvastatin and its active metabolites is lower (by approx. 25%). However, lipid effects of atorvastatin are greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Oral contraceptives: Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

1.5.1.4.6 Fertility, Pregnancy and Lactation

Pregnancy:

Atorvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction.

Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, Lipitor should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Lipitor should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Lactation:

It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. Because of the potential for serious adverse reactions, women taking Lipitor should not breast-feed their infants. Atorvastatin is contraindicated during breastfeeding

1.5.1.4.7 Effects on ability To Drive and use Machines

Negligible influence on the ability to drive and use machines.

1.5.1.4.8 Undesirable Effects

Infections and infestations: Nasopharyngitis.

Blood and lymphatic system disorders: Thrombocytopenia.

Immune system disorders: Allergic reactions.

Metabolism and nutrition disorders: Hyperglycaemia, hypoglycaemia, weight gain, anorexia.

Nervous system disorders: Headache, dizziness, paraesthesia, hypoesthesia, amnesia.

Respiratory, thoracic and mediastinal disorders: Pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders: Constipation, flatulence, dyspepsia, nausea, diarrhoea.

Skin and subcutaneous tissue disorders: Urticaria, skin rash, pruritus, alopecia.

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.

Miscellaneous: Liver function test abnormal, blood creatine kinase increased

1.5.1.4.9 Overdose

No specific treatment for atorvastatin overdose is available. In case of an overdose the patient should be treated symptomatically and supportive measures should be instituted. Liver function and serum CPK values monitored..

1.5.1.5 Pharmacological Properties

1.5.1.5.1 Pharmacodynamics Properties

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in

reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

1.5.1.5.2 Pharmacokinetic Properties

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is 98% bound to plasma proteins.

Metabolism: Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special populations:

Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease.

1.5.1.5.3 Preclinical Safety Data

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

1.5.1.6 Pharmaceutical Particulars

1.5.1.6.1 List of Excipients

Calcium Carbonate
Lactose Monohydrate
Microcrystalline Cellulose (pH 102)
Povidone (P.V.P.K.-30)
Polysorbate-80 (Tween-80)
Croscarmellose Sodium
Magnesium Stearate
Opadry White YS-1-7040
Simethicone 30%
Purified water

1.5.1.6.2 Incompatibilities

Not applicable.

1.5.1.6.3 Shelf Life

36 Months

1.5.1.6.4 Special Precautions for Storage

Store below 30°C. Protect from light & Moisture.

1.5.1.6.5 Nature and Contents of Container

10 Tablets are in Alu-Alu Blister Pack. Such 3 Alu-Alu blisters are packed in a printed carton along with packing insert.

10 Tablets are in Alu-Alu Blister Pack. Such 10 Alu-Alu blisters are packed in a printed carton along with packing insert

1.5.1.6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

1.5.1.7 Marketing Authorization Holder And Manufacturing Site Addresses

1.5.1.7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-02764-665000
Fax: +91-02764-281809
Email: info@lincolnpharma.com
Website: www.lincolnpharma.com

1.5.1.7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-02764-665000
Fax: +91-02764-281809

Email: info@lincolnpharma.com

Website: www.lincolnpharma.com

1.5.1.8 Marketing Authorization Number

To be included after obtaining first registration.

1.5.1.9 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

1.5.1.10 Date of Revision of the Text

1.5.1.11 Dosimetry (If Applicable)

Not Applicable

1.5.1.12 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable