National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Product Name: ATORVASTATIN TABLET

1.2 Strength: 20 mg

1.3 Pharmaceutical Dosage form: Tablet

2. Qualitative & Quantitative Composition

2.1 Qualitative Declaration: ATORVASTATIN TABLET

2.2 Quantitative Declaration: 20 mg

Qualitative & Quantitative Information

Batch size: 100000 Tablets

Sr. No	Ingredients	SPC	Rationale	Label Claim per tablet (in mg)	Over-ages (%)	Qty. Per Tablet (in mg)	Qty. per (1,00,000 Tablets) (in kg)
	Dry Mix blend:						
1.	Atorvastatin calcium eq. to Atorvastatin	USP	Active	21.63 = 20.00	---	21.63	2.163
2.	Lactose	BP	Diluent	15.00	---	15.00	1.500
3.	Microcrystalline Cellulose (Avicel pH102)	BP	Diluent	118.87	---	118.87	11.887
4.	Croscarmellose Sodium	BP	Disintegrant	10.00	---	10.00	1.000
5.	Magnesium Stearate	BP	Lubricant	3.00	---	3.00	0.300
6.	Colloidal Silicon dioxide	BP	Glidant	1.5		1.50	0.150
	Film Coating:						
7.	Pellcoat White	IH	Film former	4.906	--	4.906	0.491**
8.	Erythrosine lake	IH	Colouring Agent	0.094	--	0.094	0.009**
9.	Isopropyl Alcohol*	BP	Solvent	q.s.	--	q.s.	3.144**
10.	Dichloromethane*	BP	Solvent	q.s.	---	q.s.	7.956**
	TOTAL					**175.00**	**17.500**

*** Not present in final product**

**** 10% extra quantity to be taken to compensate process loss during coating.**

3. Pharmaceutical Form

Tablets

4. Clinical Particulars

4.1 Therapeutic indications

Hypercholesterolemia:

Atorvastatin Tablets are indicated as an adjunct to diet for reduction of elevated total cholesterol(total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non pharmacological measures is inadequate.

Prevention of cardiovascular disease:

Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Posology:

The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin Tablets and should continue on this diet during treatment with Atorvastatin Tablets.

The dose should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response.

The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia:

The majority of patients are controlled with Atorvastatin Tablets 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia:

Patients should be started with Atorvastatin Tablets 10 mg daily. Doses should be individualized and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg Atorvastatin once daily.

Homozygous familial hypercholesterolemia:

Only limited data are available.

The dose of Atorvastatin in patients with homozygous familial hypercholesterolaemia is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Renal impairment:

No adjustment of dose is required.

Hepatic impairment:

Atorvastatin Tablets should be used with caution in patients with hepatic impairment. Atorvastatin Tablets are contraindicated in patients with active liver disease.

Use in the elderly:

Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric use:

Hypercholesterolaemia:

For patients aged 10 years and above, the recommended starting dose of Atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be con ducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

There is limited experience in children between 6-10 years of age. Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

Other pharmaceutical forms/strengths may be more appropriate for this population.

Method of administration:

Atorvastatin Tablets are for oral administration. Each daily dose of Atorvastatin is given all at once and may be given at any time of day with or without food.

4.3 Contraindications:

Atorvastatin Tablets are contraindicated in patients:

- With hypersensitivity to the active substance or to any of the excipients of this medicinal product
- With active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

4.4 Special warnings and precautions for use:

Liver effects:

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Atorvastatin Tablets should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Skeletal muscle effects:

Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

Before the treatment:

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions and special populations including genetic subpopulations

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement:

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Whilst on treatment:

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with Atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to $\leq$5 x ULN, treatment discontinuation should be considered.

If symptoms resolve and CK levels return to normal, then re-introduction of Atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

- Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products:

Risk of rhabdomyolysis is increased when Atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of Atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. cyclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fabric acid derivates, erythromycin, niacin and ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with Atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of Atorvastatin, a lower maximum dose of Atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of Atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended.

The concurrent use of Atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of Atorvastatin may be considered during fusidic acid therapy.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statin, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Excipients

An Atorvastatin tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on Atorvastatin:

The risk might be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe.

Transport protein inhibitors:

Inhibitors of transport proteins (e.g. cyclosporine) can increase the systemic exposure of atorvastatin.

Gemfibrozil / fibric acid derivatives:

The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored.

Ezetimibe:

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin.

Colestipol:

Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when Colestipol was co-administered with Atorvastatin Tablets. However, lipid effects were greater when Atorvastatin tablets and Colestipol were co-administered than when either medicinal product was given alone.

Effect of atorvastatin on co-administered medicinal products

Digoxin:

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly.

Oral contraceptives:

Co-administration of Atorvastatin tablets with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl estradiol.

Warfarin:

Only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

4.6 Pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment.

Pregnancy:

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, Atorvastatin Tablets should not be u sed in women who are pregnant, trying to become pregnant or suspect they are pregnant.

Breastfeeding:

It is not known whether atorvastatin or its metabolites are excreted in human milk. because of the potential for serious adverse reactions, women taking Atorvastatin Tablets should not breast-feed their infants. Atorvastatin is contraindicated during breastfeeding.

Fertility:

In animal studies atorvastatin had no effect on male or female fertility

4.7 Effects on ability to drive and use machines

Atorvastatin tablets have negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following table presents the adverse reaction profile for Atorvastatin Tablets.

Infections and infestations:

Common: nasopharyngitis.

Blood and lymphatic system disorders

Rare: thrombocytopenia.

Immune system disorders

Common: allergic reactions.

Very rare: anaphylaxis.

Metabolism and nutrition disorders

Common: hyperglycaemia.

Uncommon: hypoglycaemia, weight gain, anorexia

Psychiatric disorders

Uncommon: nightmare, insomnia.

Nervous system disorders

Common: headache.

Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.

Rare: peripheral neuropathy.

Eye disorders

Uncommon: vision blurred.

Rare: visual disturbance.

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders:

Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.

Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders

Uncommon: hepatitis.

Rare: cholestasis.

Very rare: hepatic failure.

Skin and subcutaneous tissue disorders

Uncommon: urticaria, skin rash, pruritus, alopecia.

Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.

Uncommon: neck pain, muscle fatigue.

Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.

Reproductive system and breast disorders

Very rare: gynecomastia.

General disorders and administration site conditions

Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations

Common: liver function test abnormal, blood creatine kinase increased.

Uncommon: white blood cells urine positive.

Paediatric Population

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Abdominal pain

Investigations

Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

The following adverse events have been reported with some statins:

• Sexual dysfunction.

• Depression.

• Exceptional cases of interstitial lung disease, especially with long term therapy.

4.9 Overdose:

Specific treatment is not available for Atorvastatin Tablets overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. Pharmacological 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.

5.1 Pharmacokinetic Properties

Absorption:

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) 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. Atorvastatin is ≥98% bound to plasma proteins.

Biotransformation:

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 extra hepatic 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.

Paediatric: Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-Hydroxy Atorvastatin exposures.

Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

6. Pharmaceutical Particulars

6.1 List of Excipients

List of excipients

- Atorvastatin Calcium
- Lactose
- Avicel pH102
- Croscarmellose Sodium
- Magnesium Stearate

- Colloidal Silicon Dioxide
- Pellcoat White
- Erythrosine lake
- Isopropyl Alcohol
- Dichloromethane

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months

6.4 Special Precaution for Storage

Do not store above 30°C.

6.5 Nature & Content of Container

10 X 10 Tablets packed in Alu -Alu Blister.

6.6 Special precautions for disposal and other handling

7. Marketing Authorisation Holder

PELL TECH HEALTH CARE PVT. LTD.
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