**DRUG PROFILE**

3. **ATORVASTATIN CALCIUM**

The atorvastatin calcium component of is chemically described as \([R^- (R^*,R^*)]-2-(4-fluorophenyl)-\beta,\alpha\text{-dihydroxy}-5-(1-methylethyl)\text{-3-phenyl}-4[(phenylamino) carb \text{-onyl}]\text{-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is (C33H34 FN2O5) 2Ca\text{-3H2O. The Atorvastatin was selected for the development of solid self-nanoemulsifying approaches. Atorvastatin a hypolipidemic agent and is official in USP. The profile of drug is described as follows:}**

3.1. **DESCRIPTION (USP, CLARKES ANALYSIS AND MARTINDALE)**

3.1.1. Mol. Structure

![Chemical structure of Atorvastatin](image)

**Fig 3.1:** Chemical structure of Atorvastatin

3.1.2. Chemical Name: Calcium (\(\beta R,\delta R\))-2-(p-fluorophenyl)-\(\beta,\delta\text{-dihydroxy-5- isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid (1:2) trihydrate}

3.1.3. Molecular Formula: \([C_{33}H_{35}FN_2O_5]_{2}\text{Ca \cdot 3H}_{2}O\)

3.1.4. Generic Name: Atorvastatin calcium

3.1.5. Molecular Weight: 1209.4 g/mol

3.1.6. Category: Cardiovascular Agents

3.1.7. Sub-category: HMG-CoA Reductase Inhibitor

3.1.8. Percentage Purity: 98.0% - 101.0%

3.1.9. Calcium percentage: 3.3-3.6%

3.1.10. Water: 7% max
3.1.11. Loss on drying: 0.5%

3.2. **Physical Properties (USP, Clarks Analysis and Martindale)**

3.2.1. **Appearance:** White to off white amorphous powder.

3.2.2. **Solubility:** Freely soluble in methanol and soluble in dimethylsulphoxide (DMSO) and dimethyl formamide (DMF); insoluble in aqueous solution with pH less than 4.0. It is very slightly soluble in distilled water, Phosphate buffer (7.4) and acetonitrile; slightly soluble in ethanol. 20.4 µg/mL (pH 2.1), 1.23 mg/mL (pH 6.0)

3.2.3. **Stability:** Stable under ordinary conditions

3.2.4. **Pka:** 4.46

3.2.5. **Log P:** 6.36 (Octanol/Water)

3.2.6. **Melting point:** 159.2-160.7°C

3.2.7. **Storage:** To be stored in well closed, away from heat and damp places.

3.3. **Pharmacology of Atorvastatin (USP, Clarke’s Analysis and Martindale)**

Atorvastatin, a synthetic cholesterol-lowering agent, is a medicine called HMG-CoA (3 hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor. This enzyme is involved in cholesterol biosynthesis by catalyzing the conversion reaction of HMG-CoA to mevalonate. The function of lowering the amount of cholesterol leads to the result in clearing the LDP (low-density lipoprotein) cholesterol in the blood by increased LDL receptors. The calcium salt of atorvastatin is used in the treatment of primary hypercholesterolema and dyslipidemia

3.3.1. **Mechanism of Action**

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.
3.4. BIOPHARMACEUTICS AND PHARMACOKINETICS (Desager and Horsmans., 1996; Lennernas and Fager., 1997)

3.4.1. Absorption

After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% 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. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk.

3.4.2. Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is = 98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk.

3.4.3. Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. 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. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme.
3.4.4. Elimination

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration (Table 4.1).

Table 3.1: Pharmacokinetic parameters of Atorvastatin (Lennemas, H., 2003)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Parameters</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral absorption</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>2</td>
<td>Presystemic metabolism</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>3</td>
<td>Plasma protein binding</td>
<td>&gt; 98%</td>
</tr>
<tr>
<td>4</td>
<td>Volume of distribution</td>
<td>565 L</td>
</tr>
<tr>
<td>5</td>
<td>Distribution in blood (Blood cells:plasma)</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>Plasma half life</td>
<td>14 hr</td>
</tr>
</tbody>
</table>

3.4.5. Toxicity (Case study)

Rhabdomyolysis, eye hemorrhages, and liver problems

A 73-year-old, moderately obese woman with type II diabetes and hypertension she had been receiving a number of medications with no other problems and was prescribed a 10 mg daily dose of atorvastatin. 4 days later, she developed a red, itchy, painful rash (potentially life-threatening dermatosis). Treatment with atorvastatin was stopped but she still developed severe stomatitis, diffuse erythema, oedema of face, trunk and extremities, and other symptoms (Pfeiffer et al., 1998).

3.5. THERAPEUTIC USES (Schectman and Hiatt., 1996; White, C.M., 1999)

Atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin. It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias, including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and dysbetalipoproteinaemia (type III) (Maron et al., 2000;
Shepherd, J., 2001; Chong et al., 2001; Igel et al., 2002). Atorvastatin can also be effective as adjunctive therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. Atorvastatin is also used for primary prophylaxis of cardiovascular events (Cardiovascular Risk Reduction, in patients with multiple risk factors, including diabetes mellitus).

1. **Prevention of Cardiovascular Disease (Sotiriou and Cheng., 2000)**

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke.

2. **Heterozygous familial and Nonfamilial Hypercholesterolemia**

Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

3. **Elevated Serum TG Levels**

Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels.

4. **Primary Dysbetalipoproteinemia**

Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

5. **Homozygous Familial Hypercholesterolemia**
Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

6. **Pediatric Patients**

Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

- a. LDL-C remains = 190 mg/dL or
- b. LDL-C remains = 160 mg/dL and:
  - there is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patients.

3.6. **CONTRA-INDICATIONS**

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

3.7. **PRECAUTIONS**

Statins should not be given to patients with active liver disease or unexplained persistently raised serum-aminotransferase concentrations and should be discontinued if marked or persistent increases in serum-aminotransferase concentrations occur. They should be avoided during pregnancy since there is a possibility that they could interfere with fetal sterol synthesis; there have been a number of reports of congenital abnormalities associated with statins. Statins may cause myopathy and rhabdomyolysis, especially at higher doses, and they should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking drugs that increase plasma concentrations of the statin; the statin should be discontinued if creatine
phosphokinase increases significantly or if myopathy is diagnosed. Some statins, such as fluvastatin, pravastatin, rosuvastatin, and simvastatin, should be used with caution in patients with severe renal impairment.

**Children**

Bile-acid binding resins such as colestyramine have traditionally been used to treat heterozygous familial hyperlipidaemia in children and adolescents. Limited information suggests that statins are effective at lowering total cholesterol and low-density lipoprotein (LDL)-cholesterol in children older than 10 years. However, there are concerns about the potential adverse effects of statins on growth and sexual development, because these patients require life-long therapy.

**Porphyria**

Simvastatin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

**Pregnancy**

Statins are generally contra-indicated in pregnancy since there is a possibility that they might affect fetal sterol synthesis. However, a review of statin exposure in the first trimester found that out of 52 evaluable cases there were 20 reports of fetal defects, including 5 cases with severe limb anomalies, one of whom also had a CNS defect and 4 others with severe CNS defects; 1 case reported as a CNS defect was later found to have cardiac anomalies only.

**Hypersensitivity**

Patients suffering from active liver disease and some unexplained elevation of serum transaminase is reported to show hypersensitivity.

### 3.8. ADVERSE REACTIONS

The commonest adverse effects of therapy with Atorvastatin and other statins are gastrointestinal disturbances. Other adverse effects reported include headache, skin rashes, dizziness, blurred vision, insomnia, and dysgeusia. Reversible increases in serum-aminotransferase concentrations may occur and liver function should be assessed before treatment is initiated and then monitored periodically until one year after the last elevation in dose. Hepatitis and pancreatitis have been reported. Hypersensitivity reactions including anaphylaxis and angioedema have also occurred. Myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported, especially in patients taking statins
concurrently with ciclosporin, fibric acid derivatives, or nicotinic acid. Rarely, rhabdomyolysis with acute renal failure may develop.

**Effects on the blood**

Thrombocytopenia has been reported rarely with statin therapy. Serious thrombocytopenic purpura in a patient taking simvastatin resolved when therapy was stopped, although a causal role was not established. There has also been a report of an immune thrombocytopenia attributed to atorvastatin (Black et al., 1998). Adverse haematological reactions had not been noted when the patient previously received Atorvastatin.

**Effects on the eyes**

Studies in *animals* have suggested that some statins could cause cataracts. A large case-control study found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin.

**Effects on the hair**

Since its introduction in Australia 16 cases of alopecia in association with the use of simvastatin had been reported to the Adverse Drug Reactions Advisory Committee. Onset occurred between 3 days and 15 months of starting therapy. Progressive hair loss has also been reported in a woman within 6 weeks of commencing atorvastatin; the hair regrew when atorvastatin was stopped but alopecia recurred when therapy was restarted 5 months later.

**Effects on skin**

Toxic epidermal necrolysis from atorvastatin (Pfeiffer et al., 1998).

**Effects on the kidneys**

Proteinuria was reported in 10 patients taking simvastatin 40 mg daily. The protein loss was of a pattern typical for increased glomerular permeability. Renal failure due to rhabdomyolysis has been reported rarely.

**Effects on mental function**

A few cases have been reported of depressive symptoms developing in patients treated with pravastatin or simvastatin. The symptoms appeared during the first few weeks or months of
treatment. A study using lovastatin also found no effect on psychological well-being, although there was a small reduction in some measures of cognitive function. Similar reductions in some measures of cognitive function were also found with simvastatin.

**Effects on the nervous system**

A number of reports have suggested that peripheral neuropathy may be associated with statin treatment. Up to 2005, the Australian Adverse Drug Reactions Advisory Committee had received 281 reports of both sensory and sensorimotor peripheral neuropathies associated with statins. Patients had usually been taking the statin for several years before symptoms developed, and in most cases there was improvement after discontinuation, although several cases appeared to be irreversible.

**Effects on sexual function**

There have been reports of erectile dysfunction in some men receiving statins. Five men receiving simvastatin developed impotence, which resolved when fluvastatin was substituted in 4 of them. In another case, impotence occurred in a patient receiving lovastatin, and recurred when therapy was changed to pravastatin. The Australian Adverse Drug Reactions Advisory Committee had received 28 reports of impotence associated with simvastatin, which had recurred on rechallenge in 4 cases. However, a systematic review including evidence from case reports, clinical trials, and reports to regulatory agencies, supported the conclusion that statins could cause erectile dysfunction. No such effect is seen in case of atorvastatin.

**Effects on skeletal muscle**

Muscle disorders including myositis and myopathy are well known to occur with statins. Rhabdomyolysis, presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, may also occur but appears to be rare. However, fatalities have been reported. Muscle toxicity is dose related and the risk appears to be broadly similar with all of the currently marketed statins; the incidence with cerivastatin was found to be considerably higher. Patients with complex medical problems, including renal impairment and possibly endocrine disorders such as hypothyroidism, may be at increased risk of muscle toxicity; the risk is also increased by concomitant therapy with drugs that inhibit the cytochrome P450 enzyme system and increase plasma concentrations of statins. Fibrate lipid regulating drugs have also been associated with myopathy and the risk is increased if statins and fibrates are used together. The mechanism by which statins cause muscle toxicity is not clear, but it has been
suggested that depletion of ubidecarenone concentrations may be involved. Muscle weakness and soreness in a patient taking lovastatin was relieved by the administration of ubidecarenone. Other muscular disorders that have been reported in patients receiving statins include dermatomyositis in a patient receiving atorvastatin, ocular myasthenia in a patient receiving atorvastatin, and dysarthria leading to a diagnosis of myasthenia gravis in a patient receiving four different statins on separate occasions.

**Other incidence of adverse drug reactions are**

Other minor adverse drug reaction have been reported are: nausea, vomiting, headache, insomnia, anorexia, alopecia, impotence, chest pain, hypoglycaemia, abdominal pain, reversible myositis and altered liver function test etc

**3.9. DRUG-INTERACTIONS**

The most serious consequence of drug interactions with Atorvastatin and other statins is the development of myopathy or rhabdomyolysis. Drugs that can cause myopathy when given alone increase the risk of myopathy with all statins; these drugs include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by drugs that increase the plasma levels of statins by inhibiting their metabolism. Since the statins have different metabolic pathways, these interactions depend on the individual drug concerned. Simvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4, as are atorvastatin and lovastatin, and interactions may occur with drugs that inhibit this enzyme, including ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors, nefazodone, amiodarone, and verapamil; there may also be a similar interaction with grapefruit juice. Statins may also have effects on other drugs. Bleeding and increases in prothrombin time have been reported in patients taking simvastatin or other statins with coumarin anticoagulants.

**Antibacterials**

Erythromycin and other macrolides are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Increased plasma concentrations of Atorvastatin have been reported with concomitant erythromycin (Kantola et al., 1998) and increased plasma concentrations of atorvastatin have been found with erythromycin (Siedlik et al., 1999) and clarithromycin but not with azithromycin (Amsden et al., 2002).
Rifampicin, an inducer of CYP2C9 and CYP3A4, may reduce the bioavailability of fluvastatin, and has also been reported to reduce the plasma concentration of simvastatin and atorvastatin (Backman et al., 2005) There have been reports of rhabdomyolysis in patients receiving atorvastatin (Wenisch et al., 2000) or simvastatin with fusidic acid.

Anticoagulants

For reports of bleeding and increased prothrombin time in patients receiving oral anticoagulants with statins.

Antifungals

Itraconazole and ketoconazole are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Raised plasma concentrations of atorvastatin have been reported with itraconazole.

Antivirals

HIV-protease inhibitors are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may affect the metabolism of simvastatin and other statins. Studies have shown increased plasma concentrations atorvastatin with nelfinavir, and with ritonavir plus saquinavir. There has also been a report of rhabdomyolysis in a patient receiving atorvastatin with the non-nucleoside reverse transcriptase inhibitor delavirdine.

Calcium-channel blockers

Calcium-channel blockers may increase plasma concentrations of some statins, probably by inhibition of the cytochrome P450 isoenzyme CYP3A4.

Grapefruit juice

Grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4 and studies using concentrated grapefruit juice have reported increased plasma concentrations atorvastatin.

Immunosuppressants

Myopathy has been reported in patients receiving ciclosporin, and the risk may be increased when it is given with statins. There have been reports of myopathy and rhabdomyolysis in patients receiving simvastatin or atorvastatin with ciclosporin, and in patients receiving lovastatin with various immunosuppressants, often including ciclosporin. Ciclosporin has also been
reported to increase the plasma concentrations of statins, including simvastatin, atorvastatin, fluvastatin, lovastatin, and pravastatin. For the effects of statins on ciclosporin plasma concentrations.

**Lipid regulating drugs**

Myopathy and myositis are recognised adverse effects of both statins and fibric acid derivatives, including *fibrates* and *gemfibrozil*, and the risk is increased if they are given together. A similar effect has also been reported with *nicotinic acid*. The interaction between gemfibrozil and statins may also have a pharmacokinetic basis; studies have shown increased plasma concentrations of atorvastatin, lovastatin, pravastatin, and simvastatin when given with gemfibrozil.

**Proton pump inhibitors**

There is a report of rhabdomyolysis causing AV block in a patient receiving atorvastatin when *esomeprazole* and clarithromycin were added to her treatment. As symptoms started before the introduction of clarithromycin, it was thought that a possible contributory mechanism for the interaction was a reduction in the first-pass metabolism of atorvastatin due to the inhibition of p-glycoprotein by esomeprazole.

**Antacids**

Absorption of atorvastatin decreased but no effect on LDL-C reduction.

**Colestipol**

Plasma concentration of atorvastatin decreased. However LDL-C reduction is greater.

**Digoxin**

There is slight reduction in digoxin plasma level.

**Erythromycin**

Level of atorvastatin increased by 40%.

**Special precautions**

**Geriatric**

Studies with atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age = 65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults.
Gender

Studies with atorvastatin: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Insufficiency

Studies with atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary.

3.10. Analytical methodology of Atorvastatin

Different analytical methodology of the AT calcium for in-vitro and for in-vivo studies were given in the Table 3.2. Here only HPLC and LC-MS method of analysis was listed and other uv-spectrophotometric and titrimetric methods are not listed.

![Table 3.2: Different HPLC methodology for the analysis of atorvastatin](image-url)