COMMON TECHNICAL DOCUMENT

LIFEBACK ATORVASTATIN 20 (ATORVASTATIN TABLETS 20 MG)

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. Product Name: **LIFEBACK ATORVASTATIN 20 (ATORVASTATIN TABLETS 20 MG)**

2. Composition:

Each Film coated Tablet contains:

Atorvastatin Calcium USP

Eq.to Atorvastatin…….20 mg

Excipients…….q.s

Approved Colour Used

2.1. Qualitative & Quantitative Formula:

Batch size: 1, 83,000 Tablets

Sr.No	Material Name	Spec	Qty Kg /Batch	Qty mg/ Tablet	Over age	Function
1.	Atorvastatin calcium Trihydrate	USP	4.168	22.776	5%	Active
2.	Calcium carbonate (heavy)	BP	0.886	4.842	--	Diluent
3.	Lactose	BP	17.637	96.377	--	Binder
4.	Maize starch	BP	7.97	43.552	--	Glidant
5.	Povidone K 30	BP	1.015	5.546	--	Disintegrant
6.	Croscarmellose sodium	BP	1.83	10.000	--	Disintegrant
7.	Colloidal silicon dioxide	BP	0.349	1.907	--	Disintegrant
8.	Magnesium stearate	BP	0.549	3.000	--	Lubricant
	Core weight		**34.404 Kg /Batch**	**188.00 Mg /Tablet**	--	
9.	Instamoist shield (iron oxide yellow)	IHS	1.099	6.005	--	Coating agent
11.	# Isopropyl alcohol	BP	19.20 Lit	---	--	Solvent
12.	# Dichloromethane	BP	10.500 Lit	---	--	Solvent
13.	Croscarmellose sodium	BP	0.882	---	--	
	Coated weight		**35.319 Kg /Batch**	**193.00 Mg /Tablet**		

21.69 mg of Atorvastatin Calcium Trihydrate is equivalent to 20 mg of Atorvastatin

* Maximum Quantity Croscarmellose sodium required for adjusting weight of granules due to loss on drying.

Not present in the finished product

3. Pharmaceutical form

Film Coated Tablets.

Yellow coloured, Circular slightly biconvex film coated tablets having alphabetic debossing of "LB" on one side and other side scored on other side.

4. Clinical particulars

4.1 Therapeutic Indications

Hypercholesterolemia

Atorvastatin is 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 hypercholesterolemia including familial hypercholesterolemia (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.

Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial Hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if Such treatments are unavailable.

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 Dosage and administration:

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin. 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 hypercholesterolemia and combined (mixed) hyperlipidemia

The majority of patients are controlled with Atorvastatin 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 hypercholesterolemia

Patients should be started with Atorvastatin 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 sequestrate 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 hypercholesterolemia 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.

Prevention of cardiovascular disease

In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Renal impairment

No adjustment of dose is required.

Hepatic impairment

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

Hypercholesterolemia:

Paediatric use should only be carried out by physicians experienced in the treatment of Paediatric hyperlipidemia and patients should be re-evaluated on a regular basis to assess progress. 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 conducted 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 is 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 is 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. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorvastatin is recommended Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) in a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment.

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 premeasured 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 ≤ 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. ciclosporine, 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 fibric 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 statins, 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.

Paediatric use

Developmental safety in the paediatric population has not been established.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Excipients

Atorvastatin contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase 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

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of Atorvastatin and an increased risk of myopathy. The risk might also 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.

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of Atorvastatin. 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 if possible. In cases where co- administration of these medicinal products with Atorvastatin cannot be avoided lower starting and maximum doses of Atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended.

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of Atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on Atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with Atorvastatin may result in increased exposure to Atorvastatin. Therefore, a lower maximum dose of Atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

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. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous Coadministration of atorvastatin with

rifampin is recommended, as delayed administration of Atorvastatin after administration of rifampin has been associated with a significant reduction in Atorvastatin plasma concentrations. The effect of rifampin on Atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport protein inhibitors

Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of Atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on Atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended

Gemfibrozil / Fibric acid derivatives

The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. 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. Appropriate clinical monitoring of these patients is recommended.

Colestipol

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

Fusidic acid

Interaction studies with Atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction

is not known. Patients should be closely monitored and temporary suspension of Atorvastatin treatment may be appropriate.

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. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

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

Warfarin

In a clinical study in patients receiving chronic warfarin therapy, co-administration of Atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of Atorvastatin treatment. Although 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. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of Atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings should be taken into account for the paediatric population.

Fertility, pregnancy and lactation

Women of childbearing potential

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

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

Breast feeding

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

4.8 Undesirable Effects

In the Atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Atorvastatin vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on Atorvastatin Discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

Based on data from clinical studies and extensive post-marketing experience, the following table

Presents the adverse reaction profile for Atorvastatin.

Estimated frequencies of reactions are ranked according to the following convention:

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.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients.

Class Effects

− Sexual dysfunction.

− Depression.

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

− Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

Paediatric Population

The clinical safety database includes safety data for 249 paediatric patients who received Atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders

Common: headache.

Gastrointestinal disorders

Common: abdominal pain.

Investigations

Common: alanine aminotransferase increased, blood creatine phosphokinase increased.

Based on the data available, frequency, type and 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.

4.9 Overdose

In single dose volunteer studies of doses up to 800mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors,

ATC code: C10AA05

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 HMGCoA 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 hypercholesterolemia, a population that has not usually responded to lipid lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total-C (30% – 46%), LDL-C (41% – 61%), apolipoprotein B (34% – 50%), and triglycerides (14% – 33%) while producing variable Increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent In patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of Hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent Diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

<u>Homozygous familial hypercholesterolaemia</u>

In a multicenter 8 week open-label compassionate-use study with an optional extension phase of Variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial Hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was Approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect Of intensive lipid lowering with Atorvastatin 80 mg and standard degree of lipid lowering with Pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), During angiography, in patients with coronary heart disease. In this randomised, double- blind, Multicentre, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 Patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) Was -0.4% (p=0.98) in the Atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for Revascularization, non-fatal myocardial infarction, coronary death) was not investigated in this Study.

In the Atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dl ± 30) From baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 28) and in the pravastatin group, LDL-C was Reduced to a mean of 2.85 mmol/l ± 0.7 (110 mg/dl ± 26) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 26) ($p<0.0001$). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, $p<0.0001$), mean TG levels by 20% (pravastatin: -6.8%, $p<0.0009$), and mean Apolipoprotein B by 39.1% (pravastatin: - 22.0%, $p<0.0001$). Atorvastatin increased mean HDL-C By 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the Atorvastatin group compared to a 5.2% reduction in the pravastatin group ($p<0.0001$).

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated To the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in This study. Therefore, the clinical significance of these imaging results with regard to the primary And secondary prevention of cardiovascular events is unknown.

Acute coronary syndrome

In the MIRACL study, Atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with Atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in rehospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018). The other Secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

The safety profile of Atorvastatin in the MIRACL study was consistent with what is described.

Prevention of cardiovascular disease

The effect of Atorvastatin on fatal and non-fatal coronary heart disease was assessed in a Randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40– 79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/l (251 Mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first-degree relative, TC: HDL-C > 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a High risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol- based Regimen) and either Atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

The absolute and relative risk reduction effect of Atorvastatin was as follows:

Event	Relative Risk	No. of Events (Atorvastatin	Absolute Risk	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events	20%	389 vs. 483	1.9%	0.0008
and revascularization procedures	29%	178 vs 247	1.4%	0.0006
Total coronary events				

1 Based on difference in crude events rates occurring over a median follow-up of 3.3 years.

CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C $\leq$ 4.14 mmol/l (160 mg/dl) and TG $\leq$ 6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, micro albuminuria or macro albuminuria. Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk	No. of Events (Atorvastatin	Absolute R i s k	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHDdeath, unstable angina, CABG, PTCA,revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (Fatal and non- fatal)	48%	21 vs. 39	1.3%	0.0163

1 Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart Disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the Placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, theeffect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21– 92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71–0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All-cause mortality was 9.1% (216/2365) for atorvastatin Versus 8.9% (211/2366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of haemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

− The risk of haemorrhagic stroke was increased in patients who entered the study with prior Haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84–19.57), and the risk of ischemic stroke was similar between groups (3/45 for Atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27–9.82).

− The risk of haemorrhagic stroke was increased in patients who entered the study with prior Lacunar infarct (20/708 for Atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71–14.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57–1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive Atorvastatin 80 mg/day. All-cause mortality was 15.6% (7/45) for Atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior haemorrhagic stroke. All-cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

Paediatric Population

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 6–17 years old

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of Atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage ≥ 2.

The initial dose of Atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of < 3.35 mmol/L at Week 4 and if atorvastatin was well tolerated. Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the

first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10–17 years old

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10–17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 3.36 mmol/l. Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.93–9.96 mmol/l) in the placebo group during the 26-week double-blind phase. An additional paediatric study of Atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10–18 years demonstrated that Atorvastatin (N=25) caused a significant reduction in LDL-C at week 26 ($p<0.05$) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL cholesterol was lowered by 36%.

The long-term efficacy of Atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

The European Medicines Agency has waived the obligation to submit the results of studies with Atorvastatin in children aged 0 to less than 6 years in the treatment of heterozygous hypercholesterolaemia and in children aged 0 to less than 18 years in the treatment of homozygous familial hypercholesterolaemia, combined (mixed) hypercholesterolaemia, primary

hypercholesterolaemia and in the prevention of cardiovascular events for information on paediatric use).

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.

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: In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥ 2 (N=24) Paediatric patients (ages 6–17 years) with heterozygous familial hypercholesterolemia and Baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film coated

Atorvastatin tablets once daily, respectively. Body weight was the only significant Covariate in Atorvastatin population PK model.

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-hydroxyatorvastatin exposures.

Gender: Concentrations of Atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax 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.

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 (Child-Pugh B).

SLCO1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS:

Raw materials
Calcium carbonate
Lactose
Maize starch
Povidone K 30
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Instamoist shield (iron oxide yellow)
Isopropyl alcohol
Dichloromethane

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
36 Months

6.4 Special Precautions for Storage
Store at temperature below 30°C in a dry place. Protect from light.

Keep out of reach of Children.

6.5 Nature and Contents of Container

3 X 10 TABLETS ALU/ALU BLISTER

Yellow colour, circular biconvex film coated tablets with score on middle of one side and 'LB' debossing on other side. 3 Tablets packed in Alu/Alu blister. 10 such blisters packed in a printed carton with pack insert. Such cartons packed in a 7 ply corrugated box.

6.5 Special Precautions for Disposal and Other Handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

MMC Healthcare Ltd.

No. 34-B, SIDCO Industrial Estate,

Thirumazhisai, Chennai – 600 124, India.