SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

1.1 Product Name

Atorvastatin Calcium Tablets 20mg

1.2 Strength

Atorvastatin Calcium USP
Equivalent to Atorvastatin 20 mg

1.3 Pharmaceutical Form

Tablet for Oral Administration

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Each Film coated Tablets Contains:
Atorvastatin Calcium USP
Equivalent to Atorvastatin 20 mg

2.2 Quantitative Declaration

Sr. No	Ingredients	Specification	Quantity per Tablet (mg)	Overages (%)	Standard Quantity Per Batch (Kg)	Functions
CORAE TABLET						
1.	**Atorvastatin Calcium***	USP	22.60	NA	2.260	Active Pharmaceutical Ingredient
2.	Microcrystalline Cellulose Phosphate PH 101	USP	50.00	NA	5.000	Disintegrant
3.	Lactose	USP	40.56	NA	4.056	Diluent

4.	Corn Starch (for dry mixing)**	USP	26.34	10%	2.897	Diluent
5.	Corn Starch (for binder paste)**	USP	13.00	10%	1.430	Binder
6.	Sodium benzoate	USP	0.50	NA	0.050	Preservative
7.	Magnesium Stearate	USP	3.00	NA	0.300	Lubricant
8.	Talc	USP	6.00	NA	0.600	Glidant
9.	Colloidal Silicon Dioxide	USP	2.00	NA	0.200	Glidant
10.	Sodium Starch Glycolate	USP	6.00	NA	0.600	Disintegrant
11.	Croscarmellose Sodium	USP	10.00	NA	1.000	Disintegrant
12.	Purified water@	USP	qs	NA	qs	Solvent
Average weight of the uncoated Tablets			**180.00 mg**		**18.00kg**	
FILM COATING* **						
13.	Ready mix film coating erythrosine lake	In-house	3.00	60%	0.480	Coating Material
14.	Isopropyl Alcohol@	USP	30.00	NA	3.000	Solvent
15.	Methylene Chloride@	USP	60.00	NA	6.000	Solvent
Average weight of the film coated Tablets			**183.0mg**		**18.300kg**	

* The quantity of API may vary with Assay and LOD.
** Overages in Corn starch have been added to compensate the drying loss.
*** Overages in coating materials have been added to compensate the process loss.
$ The quantity of Corn starch USP is to be calculated on the actual quantity of API calculated on the basis of assay.
@ Does not remain in the finished product, removed during the process.
Note: Each 22.60 mg Atorvastatin Calcium USP = 20.00 mg of Atorvastatin.

3. Pharmaceutical Form

Description:

Pink colour, circular, biconvex, film coated tablets, having central break line on one side & other side plain.

Rational of break line

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses, 'the tablet can be divided into equal halves'.

4. Clinical Particulars

4.1 Therapeutic indications

Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with Updated January 2015 Page 3 primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum triglyceride levels (Fredrickson Type IV), and for patients with dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet. Atorvastatin is also indicated for the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate.

Prevention of Cardiovascular Disease 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

4.2 Posology and Method of Administration

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat underlying medical problems. The patient should continue on a standard cholesterol-lowering diet during treatment with atorvastatin. The dosage range is 10 to 80 mg once daily. Doses may be given any time of the day, with or without food.

Homozygous Familial Hypercholesterolemia

Most patients responded to 80 mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

Use in Patients with Renal Insufficiency

Renal disease has no influence on the plasma concentrations or on the LDL-C reduction with atorvastatin. Thus, no adjustment of the dose is required.

Use in the Elderly

No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Use in Children

Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80mg/day for one year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.

4.3 Contraindications

No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Use in Children

Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80mg/day for one year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.

4.4 Special warning and precautions for use

Hepatic Effects

As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10, 20, 40 and 80 mg.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin.

Skeletal Muscle Effects

Myalgia has been reported in atorvastatin-treated patients. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias,

muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Hemorrhagic Stroke

There is higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo. Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke.

4.5 Interaction with other medicinal products and other forms of interactions

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin or cytochrome P450 3A4 inhibitors (eg erythromycin and azole antifungals).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Erythromycin/Clarithromycin

Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

Itraconazole

Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC.

Grapefruit juice

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Antacids

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.

Antipyrine

Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Azithromycin

Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

Amlodipine

Co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

4.6 Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy. Women of childbearing potential should use adequate contraceptive measures. Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been

informed of the potential hazards to the fetus. Atorvastatin is contraindicated while breast-feeding. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed.

4.7 Effects on ability to drive and use machine

LUMISTEROL-20 (Atorvastatin Calcium Tablets 20 mg)has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. Most frequent adverse effects associated with atorvastatin therapy Infections and infestations: nasopharyngitis Metabolism and nutrition disorders: hyperglycemia Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis Gastrointestinal disorders : nausea, diarrhea, dyspepsia, flatulence Musculoskeletal and connective tissue disorders : arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling Investigations: liver function test abnormal, blood creatine phosphokinase increased.

4.9 Overdose

LUMISTEROL-20 (Atorvastatin Calcium Tablets 20 mg) is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Atorvastatin calcium is a synthetic lipid-lowering agent, which is an inhibitor of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

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 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 in patients with homozygous familial hypercholesterolemia, a population that has not normally responded to lipid-lowering medication.

5.2 Pharmacokinetic Properties

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within one to two hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared with solutions. The absolute bioavailability of atorvastatin 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.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is≥98% bound toplasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various betaoxidation 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 hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme.

Excretion

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic 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.

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

Microcrystalline cellulose, Lactose, Corn Starch, Sodium benzoate,Magnesium Stearate, Talc, ColloidalSilicon Dioxide, Sodium Starch Glycolate, Croscarmellose Sodium, Ready mix film coating white colour.

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for storage

Store at a temperature not exceeding 30^0C.Protected from light & moisture.

6.5 Nature and Contents of Container

10 Tablets packed in Alu-Alu blister

6.6 Special precautions for disposal

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

7. Marketing Authorization Holder

GLOBAL ORGANICS LTD.
PLOT-868, KM-34,
Lagos Abeokuta express way,
Lagos state,
NIGERIA

Marketing Authorization Numbers

NA

8. Date of revision of text

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