1.3.1
Summary of Product Characteristics (SmPC)

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Enclosed in the following pages

Summary of Product Characteristic

1 Name of the medicinal product

Product Name : **COLESTRIM Tablets**
(Fenofibrate 160 mg)

1.1 Strength :160 mg

1.2 Pharmaceutical Dosage Form : Oral Tablets

2 Quality and Quantitative composition

Ingredients	Specification	Quantity /tab (mg)
Fenofibrate	BP	160.0
Lactose Monohydrate	BP/Ph Eur	412.3
Pregelatinised Starch	BP/Ph Eur	75.0
Croscarmellose Sodium	BP/Ph Eur	18.0
Crospovidone	BP/Ph Eur	18.0
Povidone K90	IP/BP/Ph Eur	6.00
Sodium Lauryl Sulphate	BP/Ph Eur	3.20
Magnesium Stearate	IP/BP/Ph Eur	1.50
Purified Talc	IP/BP/Ph Eur	6.00
Purified Water	IP/USP/Ph Eur	q.s.
Hypromellose E5	IP/BP/Ph Eur	12.20
Polysorbate 80	BP/Ph Eur	1.50
Titanium Dioxide	IP/BP/Ph Eur	1.30
Isopropyl Alcohol	IP/BP/Ph Eur	q.s.
Dichloromethane	BP/Ph Eur	q.s.

3 Pharmaceutical Form

Oral Tablet

4 Clinical Particulars

4.1 Therapeutic indications

Treatment of Hvper cholesterolemia
COLESTRIM is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types II a and II b). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate.

Treatment of Hvoertriglyceridemia
COLESTRIM is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

4.2 Posology and method of administration

Patients should be placed on an appropriate lipid-lowering diet before receiving COLESTRIM, and should continue this diet during the treatment with COLESTRIM. COLESTRIM tablets should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of Fenofibrate is 160 mg day.

For adult patients with hypertriglyceridemia, dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at4 to 8 week intervals.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of Fenofibrale if lipid level falls significantly below the targeted range.

4.3 Contraindications

Fenofibrate is contraindicated in patients who exhibit hypersensitivity to Fenofibrate or to any excipients. Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis and patients with unexplained persistent liver function abnormality. Fenofibrate is also contraindicated in patients with pre-existing gall bladder disease.

4.4 Special warning and precautions for use

Precautions:
Initial therapy: Laboratory should be done to ascertain that the lipid levels are consistently abnormal before instituting Fenofibrate therapy. Every attempt should be made to control

serum lipids with appropriate diet, exercise, weight loss in obese patients and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (blockers, thiazides, estrogens) should be discontinued or changed if possible, prior to consideration of triglyceride lowering drug therapy.
Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of Fenofibrate. Therapy should be withdrawn in patients who do not have an adequate response
after two months of treatment with the maximum recommended dose of 160 mg per day.

Pancreatitis has been reported in patients taking Fenofibrate, gemfibrozil and clofibrate. The occurrence may represent a failure of efficacy in patients with severe hyper triglyceridaemia, a direct drug effect, or a secondary phenomenon medicated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity reactions· Acute hypersensitivity reactions include severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with Fenofibrate, including rare spontaneous reports of Stevens Johnson syndrome and toxic epidermal necrolysis.

Hematological changes: Mild to moderate hemoglobin, hematocrit and white blood cell decreases have been observed in patients following initiation of Fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance. Periodic blood counts are recommended during the first 12 months of Fenofibrate administration.

Liver function· Fenofibrate at doses equivalent to 107 mg to 160 mg per day has been associated with increases in serum transaminases. When transaminase determinations were followed either after discontinuation treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increase I transaminases related to Fenofibrate therapy appear to be dose related.

Hepatocellular, chronic active and cholestatic hepatitis associated with Fenofibrate therapy have been reported after exposure to weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis. Regular periodic monitoring of liver function including serum ALT (SGPT) should be performed for the duration of therapy with Fenofibrate and therapy discontinued if enzyme levels persist above three times the normal limit.

Skeletal muscle: The use of fibrates alone, including Fenofibrate may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomlosis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and or marked elevations of creatinine phosphokinase levels. Patients should be advised to report prompt unexplained muscle pain, tenderness or weakness, particularly if

accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms and Fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated, Fenofibrate therapy should be discontinued if gallstones are found.

4.5 Interaction with other medicinal products and other forms of interactions

-Oral anticoagulants: Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third althe start of treatment and then gradually adjusted if necessary according to INR (International Normalised RatiO) monitoring. Therefore, this combination is not recommended.

-Cyclosporin: Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. The renal function ofthese patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMG-CoA reductase inhibitors and other fibrates: The risk of serious muscle toxicity is increased if a fibrate is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closelyfor signs of muscle toxicity.

4.6 Pregnancy and lactation

Pregnancy category C: Fenofibrate should not be used during pregnancy.

Nursing Mothers:
Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenecity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatrics:
Safety and effectiveness in pediatric patients have not been established.

Geriatrics:
Fenofibric acid is known to be substantially excreted by the kidney and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

4.7 Effects on ability to drive and use machine

Not available

4.8 Undesirable effects

The Adverse effects are mild and fugitive
Common: 1/1oo<ADR<1/10
Gastrointestinal: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhea, flatulence).
Hepato-biliary: Moderate levels or serum transaminases.
Uncommon: 1/1000<ADR < *1/100*
Liver: Development of gallstones.
Skin: rashes, urticaria or photosensitivity reactions
Testing: increases in serum creatinine and urea
Rare: 1/10000 <ADR< 1/1000
.Hair;.alopecia
Muscles: diffuse myalgia, myositis, muscular cramps and weakness
Blood;. decrease in haemoglobin and leukocytes
Nervous system: sexual asthenia
Very rare: < 1110000
Gastrointestinal: Cases of pancreatitis have been reported during treatment with Fenofibrate

4.9 Management of overdose

There is no specific treatment for overdose with fenofibrate. General supportive care of the patients is indicated, including monitoring of vital signs and observation of clinical status, should an overdosage occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage, usual precautions should be achieved by emesis or gastric lavage, and usual precautions should be observed to maintain the airway. Because Fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

5 Pharmacological Properties.

5.1 Pharmacodynamic Properties

Mechanism of action

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are medicated via activation of Peroxisome Proliferated Receptor type alpha (PPAR). Through activation of PPAR, Fenofibrale increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII (an inhibitor of lipoprotein lipase activity). The resulting fall in Triglycerides (TGs) produces an alteration in the size and composition of low density Lipoproteins (LDL) from small, dense particles (which are thought to be atherogenic due to

their susceptibility to oxidation) to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR also induces an increase in the synthesis of apoproteins A I and AIl and HDL cholesterol.

The above stated effects of Fenofibrate on lipoproteins leads to a reduction in very low-end low density fractions (VLDL & LDL) containing apoprotein A I &A II (Apo I &Apo II).
In addition, through modulation of synthesis and the catabolism of VLDL fractions, Fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease. Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

5.2 Pharmacokinetic Properties

Fenofibrate is well absorbed from the gastrointestinal tract. Peak plasma levels of Fenofibrate acid occure within 6 to 8 hours after administration. The absorption of Fenofibrate tablets is increased by approximately 35% underfed as compared to fasting conditions.
In healthy volunteers, steady-state plasma levels of Fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately99% in normal and hyper lipidemic patients.
Following oral administration, Fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, Fenofibric acid is primarily conjugated with glucoronic acid and then excreted in urine. A small amount of Fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite, which is in tum, conjugated with glucoronic acid and excreted in the urine. In-vivo metabolism data indicate that neither Fenofibrate nor Fenofibric acid undergo oxidative metabolism (eg. Cytochrome P450)to a significant extent. Fenofibrate is mainly excreted in the urine in the form of metabolites, primarily Fenofibric acid & Fenofibric acid glucoronide. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled Fenofibrate appeared in the urine, primarily as Fenofibric acid & its glucoronate conjugate & 25% was excreted in the feces. Fenofibric acid is eliminated with a half life of20 hours, allowing once daily administration in a clinical setting.

5.3 Preclinical safety Data

Not available

6 Pharmaceutical Particulars

6.1 List of excipients

Lactose Monohydrate , Pregelatinised Starch , Croscarmellose Sodium , Crospovidone , Povidone K90 , Sodium Lauryl Sulphate , Magnesium Stearate , Purified Talc , Hypromellose E5 , Polysorbate 80 , Titanium Dioxide

6.2 Incompatibilities

Not available.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store below 30 °C in a dry place.

6.5 Nature and contents of container

3 blisters of 10 tablets in carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7 Marketing Authorization Holder

Mega Lifesciences Nigeria Ltd

8. Marketing Authorization Numbers

A4-1962

9 Date of first authorization/ renewal of the authorization

Jan 2016

10 Date of revision of the text
