Front

Size: 210 x 240 mm

210 mm

240 mm

FENOFIBRATE + ATORVASTATIN

FIBROVAS

(160 mg / 10 mg Tablets)

Lipid modifying agents, HMG-CoA-reductase inhibitors

PRODUCT NAME:
FIBROVAS

DOSAGE FORM AND STRENGTH:
Fenofibrate 160mg and Atorvastatin 10mg Tablets

PHARMACOLOGIC CATEGORY:
Lipid modifying agents, HMG-CoA-reductase inhibitors/Cholesterol and Triglycerides Reducers / Fibrates

PRODUCT DESCRIPTION:
Yellow coloured, circular, biconvex, film-coated tablet with break-line on one surface and plain on the other surface.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Fenofibrate BP .....160 mg
Atorvastatin Calcium USP equivalent to Atorvastatin ..... 10 mg

Pharmacodynamics
Fenofibrate:
The effects of fibrates on blood lipids are mediated by their interaction with peroxisome proliferator activated receptors (PPARs), which regulate gene transcription. Three PPAR isotopes (α, β, and γ) have been identified. Fibrates bind to PPARα, which is expressed primarily in the liver and brown adipose tissue and to a lesser extent in kidney, heart, and skeletal muscle. Fibrates reduce triglycerides through PPARα-mediated stimulation of fatty acid oxidation, increased LPL synthesis, and reduced expression of apo C-III. An increase in LPL would enhance the clearance of triglyceride-rich lipoproteins. A reduction in hepatic production of apo C-III, which serves as an inhibitor of lipolysis processing and receptor-mediated clearance, would enhance the clearance of VLDL. Fibrate-mediated increases in HDL-C are due to PPARα stimulation of apoA-I and apoA-II expression, which increases HDL levels. Fenofibrate is more effective than gemfibrozil at increasing HDL levels.
Atorvastatin:
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are
incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL cholesterol (LDL-C), and Apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Pharmacokinetics:
Absorption
Fenofibrate: Fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled Fenofibrate appeared in urine, primarily as Fenofibric acid and its glucuronide conjugate, and 25% was excreted in the feces. Peak plasma levels of Fenofibric acid occur within 6 to 8 hours after administration. The absorption of Fenofibrate is increased when administered with food. With micronized Fenofibrate, the absorption is increased by approximately 35% under fed as compared to fasting conditions.
Atorvastatin: Atorvastatin is rapidly absorbed after oral administration; 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.
Distribution and Protein Binding
Fenofibrate: In healthy volunteers, steady-state plasma levels of Fenofibric acid were shown to be achieved within 5 days of dosing with single oral doses equivalent to 67 mg Fenofibrate and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidaemia subjects.
Atorvastatin: 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.
Metabolism
Fenofibrate: Following oral administration, Fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, Fenofibric acid; no unchanged Fenofibrate is detected in plasma. Fenofibric acid is primarily conjugated with glucuronic 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 turn, conjugated with glucuronic acid and excreted in urine. *In vivo* metabolism data indicate that neither Fenofibrate nor Fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.
Atorvastatin: Atorvastatin is extensively metabolized to ortho- and Para hydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.
Elimination
Fenofibrate: After absorption, Fenofibrate is mainly excreted in the urine in the form of metabolites, primarily Fenofibric acid and Fenofibric acid glucuronide. After administration of radiolabelled Fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.
Atorvastatin: 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.

INDICATIONS:
Combined hyperlipidaemia Fibrovas 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 these patients. Lipid altering agents should be used in addition to diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate.

DOSAGE AND MODEL ROUTE OF ADMINISTRATION:
Patients should be placed on an appropriate lipid-lowering diet before receiving Fibrovas, and should continue this diet during treatment. Fibrovas should be given with meals, thereby optimizing the bioavailability of the medication. The recommended dosage is one tablet once daily.

MODE OF ADMINISTRATION: Oral Use

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)
Fenofibrate: Contraindicated in patients who exhibit hypersensitivity to Fenofibrate. 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 preexisting gallbladder disease.
Atorvastatin: Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication

PRECAUTIONS AND WARNINGS:
Fenofibrate:
Liver Function: Fenofibrate has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. The incidence of increases in transaminase related to Fenofibrate therapy appears to be dose related. Hepatocellular, chronic active and cholestatic hepatitis associated with Fenofibrate therapy have been reported after exposures of 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.
Cholelithiasis: Fenofibrate 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.
Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with Fenofibrate because of the potentiation of coumarin type anticoagulants in prolonging the prothrombin time/INR.
Concomitant HMG-CoA Reductase Inhibitors: The combined use of Fenofibrate and HMGCoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. The use of Fenofibrate may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving Fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, Fenofibrate therapy should be stopped.
Mortality: The effect of Fenofibrate on coronary heart disease morbidity and mortality and no cardiovascular mortality has not been established.
Pancreatitis: Pancreatitis has been reported in patients taking Fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.
Hypersensitivity Reactions: Acute hypersensitivity reactions including 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.
Skeletal Muscle: The use of Fenofibrate may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, 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 creatine phosphokinase levels.
Atorvastatin:
Liver Dysfunction: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of

patients who received atorvastatin in clinical trials.
It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semi-annually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times 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. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of Atorvastatin.
Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin. Uncomplicated myalgia has been reported in atorvastatin-treated patients. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).
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 other underlying medical problems.

DRUG INTERACTIONS:
Fenofibrate:
In vitro studies using human liver microsomes indicate that Fenofibrate and Fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to moderate inhibitors of CYP2C9 at therapeutic concentrations. Potentiation of coumarin-type anti-coagulants has been observed with prolongation of the prothrombin time/INR. Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, Fenofibrate should be taken at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption.
Atorvastatin:
- The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. cyclosporine, erythromycin, clarithromycin, and azole antifungals).
- 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.
- Concomitant administration of atorvastatin with clarithromycin, Erythromycin, Protease inhibitors, Itraconazole, Diltiazem, Grapefruit juice, Cyclosporine, resulted in increase in atorvastatin AUC.
- Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampin), Antacid, Colestipol, can lead to variable reductions in plasma concentrations of atorvastatin.

Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

PREGNANCY AND LACTATION:
Fenofibrate:
There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.
Atorvastatin:
Safety in pregnant women has not been established. Hence Atorvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Atorvastatin, it should be discontinued and the patient advised again as to the potential hazards to the fetus. Because of the potential for adverse reactions in nursing infants, women taking Atorvastatin should not breast-feed.

ADVERSE EFFECTS:
Fenofibrate:
Body as a Whole: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.
Cardiovascular System: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extra systoles, myocardial infarct, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extra systoles, and atrial fibrillation.
Digestive System: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal haemorrhage, liver fatty deposit, eructation, and diarrhea.
Endocrine System: Diabetes mellitus.
Hemic and Lymphatic System: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
Metabolic and Nutritional Disorders: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricaemia, and peripheral edema.
Musculoskeletal System: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.
Nervous System: Dizziness, insomnia, depression, vertigo, libido decreased anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
Respiratory System: Pharyngitis, bronchitis, coughs increased, dyspnoea, asthma, pneumonia, laryngitis, and sinusitis.
Skin and Appendages: Rash, pruritus, urticaria, acne, sweating, skin disorder, alopecia, contact dermatitis, herpes simplex, maculo-papular rash, nail disorder, and skin ulcer.
Special Senses: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
Urogenital System: Urinary frequency, prostatic disorder, kidney function abnormal, urolithiasis, gynaecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.
Atorvastatin:
The following adverse events were reported:
Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.
Digestive System: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal haemorrhage, esophagitis, eructation, Glossitis, mouth ulceration, anorexia, stomatitis, Cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum haemorrhage, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.
Respiratory System: Bronchitis, rhinitis, pneumonia, dyspnoea, asthma, epistaxis.
Nervous System: Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional liability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypaesthesia, hypertonia.
Musculoskeletal System: Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tedious contracture, myositis.
Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhoea, skin ulcer.
Urogenital System: Urinary tract infection, haematuria, albuminuria, urinary frequency, cystitis, impotence, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine haemorrhage.
Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye haemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.
Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.
Metabolic and Nutritional Disorders: Peripheral edema, hyperglycaemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.
Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

OVERDOSE AND TREATMENT:
Fenofibrate:
There is no specific treatment for overdose with Fenofibrate. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because Fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.
Atorvastatin:
There is no specific treatment for atorvastatin over dosage. In the event of an overdose, 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.

STORAGE CONDITION:
STORE AT TEMPERATURES NOT EXCEEDING 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Tablet
Alu-Alu Blister pack of 10's (Box of 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):
Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:
Marketing Authorization Holder
Brown & Burk Philippines Inc
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:
MICRO LABS LIMITED
No. 92, Sipcot Industrial Complex,
Hosur – 635 126, India

CAUTION STATEMENT:
FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:
"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sigh of Adverse Drug Reaction.

REGISTRATION NUMBER:
DR-XY46755

DATE OF FIRST AUTHORIZATION:
24 October 2019

DATE OF REVISION OF PACKAGE INSERT:
Mar. 2020

EXG-ML01I-****