3.1 DRUGS PROFILE

3.1.1 Atorvastatin Calcium

3.1.1.1 PHYSICAL PROPERTIES

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin calcium is \[\text{[R-}(-\text{R}^*,\text{R}^*)\text{-}2\text{-}(4\text{ fluorophenyl})\text{-}b,\text{ d- dihydroxy -5- (1- methylethyl) -3- phenyl -}4\text{- [(phenylamino) carbonyl] -1 Hpyrrole -1- heptanoic acid, calcium salt (2:1) trihydrate}.\] The empirical formula of atorvastatin calcium is \((\text{C}_{33}\text{H}_{34}\text{FN}_{2}\text{O}_{5})_2\text{Ca}\cdot3\text{H}_2\text{O}\) and its molecular weight is 1209.42. Its structural formula is:

Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

3.1.1.2 CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacodynamics

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response.

Pharmacokinetics

Absorption

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**

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

**Metabolism**

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

**Excretion**

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.

**Special Populations**

**Geriatric**

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

**Pediatric**

Pharmacokinetic data in the pediatric population are not available.

**Gender**

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC).

**Renal Insufficiency**

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

**Hemodialysis**
While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency
In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

3.1.1.3 INDICATIONS AND USAGE

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 calcium is indicated to:

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

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

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

In patients with clinically evident coronary heart disease, Atorvastatin calcium is indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

Hypercholesterolemia
Atorvastatin calcium is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet;
4. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable;

3.1.1.4 CONTRAINDICATIONS
Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication.

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

3.1.1.5 WARNINGS

Liver Dysfunction
HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. 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
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).

3.1.1.6 DRUG INTERACTIONS

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, andazole antifungals) (see WARNINGS, Skeletal Muscle).

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.

Clarithromycin
Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atorvastatin AUC.

**Erythromycin**
In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4.

**Combination of Protease Inhibitors**
Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg+100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC.

**Itraconazole**
Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with a 2.5–3.3-fold increase in atorvastatin AUC.

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

**Cimetidine**
Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

**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).

**Cyclosporine**
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg.

**Inducers of cytochrome P450 3A4**
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, 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.

**Antacid**
When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased 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.

**Colestipol**
Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.
Digoxin
When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives
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.

Warfarin
Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Amlodipine
In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

3.1.1.7 DOSAGE FORMS
Atorvastatin Tablets 10, 20, 40, 80 mg
Chewable Tablets 5, 10, 20, 40 mg
3.1.2 Fenofibrate

3.1.2.1 PHYSICAL PROPERTIES
Fenofibrate is a lipid regulating agent available as hard gelatin capsules for oral administration. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:

![Chemical Structure of Fenofibrate](image)

The empirical formula is C_{20}H_{21}O_{4}Cl and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

3.1.2.2 CLINICAL PHARMACOLOGY
Mechanism of Action
The active moiety of Fenofibrate is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting decrease in triglycerides produces an alteration in the size and composition of 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 PPARα also induces an increase in the synthesis of apolipoproteins A-I, A-II and HDL-cholesterol.

Pharmacodynamics
Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the body to fenofibric acid which is the active constituent measurable in the circulation. In a bioavailability study with Fenofibrate capsules 200 mg, following single-dose administration, the plasma concentration (AUC) for the parent compound fenofibrate was approximately 40 μg/mL compared to 204 μg/mL for the metabolite, fenofibric acid. In the same study, the half-life was observed to be 0.91 hrs for the parent compound versus 16.76 hrs for the metabolite.

Pharmacokinetics
Absorption
The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within approximately 5 hours after oral administration.
Chapter 3: Materials

The absorption of fenofibrate is increased when administered with food. With Fenofibrate, the extent of absorption is increased by approximately 58% and 25% under high-fat fed and low-fat fed conditions as compared to fasting conditions, respectively.

In a single dose and multiple dose bioavailability study with Fenofibrate capsules 200 mg, the extent of absorption (AUC) of fenofibric acid, the principal metabolite of fenofibrate, was 42% larger at steady state compared to single-dose administration. The rate of absorption (Cmax) of fenofibric acid was 73% greater after multiple-dose than after single-dose administration.

The extent of absorption of Fenofibrate in terms of AUC value of fenofibric acid increased in a less than proportional manner while the rate of absorption in terms of Cmax value of fenofibric acid increased proportionally related to dose.

Distribution

Upon multiple dosing of fenofibrate, fenofibric acid steady state is achieved after 5 days. Plasma concentrations of fenofibric acid at steady state are slightly more than double those following a single dose. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; unchanged fenofibrate is detected at low concentrations in plasma compared to fenofibric acid over most of the single dose and multiple dosing periods.

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 vitro and in vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabeled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in feces. Fenofibric acid is eliminated with a half-life of approximately 20 hours allowing once daily administration in a clinical setting.

Special Populations

Geriatrics: In elderly volunteers 77 to 87 years of age, the apparent oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that an equivalent dose of Fenofibrate can be used in elderly subjects with normal renal function, without increasing accumulation of the drug or metabolites [see Dosage and Administration (2.4) and Use in Specific Populations (8.5)].

Pediatrics: Pharmacokinetics of Fenofibrate has not been studied in pediatric patients.

Gender: No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race: The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability.
Renal Impairment: The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate and severe renal impairment. Patients with severe renal impairment (creatinine clearance \([CrCl] \leq 30 \text{ mL/min}\) showed 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild (\(CrCl 50-80 \text{ mL/min}\)) to moderate renal impairment (\(CrCl 30-50 \text{ mL/min}\)) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Fenofibrate should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

Hepatic Impairment: No pharmacokinetic studies have been conducted in patients having hepatic impairment.

3.1.2.3 INDICATIONS AND USAGE
Fenofibrate is indicated as an adjunct to diet and other non pharmacological treatment (e.g. exercise, weight reduction) for the following:

- Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.
- Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.
- Mixed hyperlipidaemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.

3.1.2.4 CONTRAINDICATIONS
Fenofibrate is contraindicated in children, in patients with severe liver dysfunction, gallbladder disease, biliary cirrhosis, severe renal disorders and in patients hypersensitive to fenofibrate or any component of this medication, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen. Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia. Use during pregnancy and lactation. This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

3.1.2.5 WARNINGS
Secondary causes of dyslipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is initiated.
Response to therapy should be monitored by determination of serum lipid values (total cholesterol, LDL-C, triglycerides). If an adequate response has not been achieved after several months (e.g. 3 months) complementary or different therapeutic measures should be considered.

Renal impairment
In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. In this case, Fenofibrate 67 mg capsules should be used, e.g. 2 Fenofibrate 67 mg capsules daily for creatinine clearance levels of <60 ml/min and 1 Fenofibrate 67 mg capsule daily for creatinine clearance levels of <20 ml/min.
It is recommended that creatinine is measured during the first three months after initiation of treatment and thereafter periodically. Treatment should be interrupted in case of an increase in creatinine levels > 50% of (upper limit of normal). Use of Fenofibrate 67 mg capsules are also to be preferred in elderly patients with renal impairment where dosage reduction may be required.

**Serum Transaminases**
Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment. However, it is recommended that serum transaminases should be monitored every three months during the first twelve months of treatment. Treatment should be interrupted in the event of ALAT (SGPT) or ASAT (SGOT) elevations to more than 3 times the upper limit of the normal range or more than one hundred international units.

**Pancreatitis**
Pancreatitis has been reported in patients taking fenofibrate (see section 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

**Myopathy**
Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminaemia and previous renal insufficiency. Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or family history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may also be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with fenofibrate should be stopped.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

For hyperlipidaemic patients taking oestrogens or contraceptives containing oestrogen it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).

### 3.1.2.6 DRUG INTERACTIONS

**Coumarin Anticoagulants**
Potentiation of coumarin-type anticoagulant effect has been observed with prolongation of the PT/INR. Caution should be exercised when Fenofibrate is given in conjunction with coumarin anticoagulants. Fenofibrate may potentiate the anticoagulant effect of these agents resulting in prolongation of the PT/INR. To prevent bleeding complications, frequent monitoring of PT/INR and dose adjustment of the oral
anticoagulant as recommended until the PT/INR has stabilized [see Warnings and Precautions (5.6)].

**Immunosuppressants**
Immunosuppressant agents such as cyclosporine and tacrolimus can impair renal function and renal excretion is the primary elimination route of fibrate drugs including Fenofibrate. When immunosuppressants and other potentially nephrotoxic agents are co-administered with Fenofibrate, the lowest effective dose of Fenofibrate should be employed and renal function should be monitored.

**Bile-Acid Binding Resins**
Since bile-acid binding resins may bind other drugs given concurrently, patients should take Fenofibrate at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption.

3.1.2.7 **DOSAGE FORMS**
- Fenofibrate Capsule 67 mg
- Fenofibrate Capsule 160 mg
- Fenofibrate Capsule 200 mg
- Fenofibrate Capsule 267 mg
3.1.3 Ezetimibe

3.1.3.1 PHYSICAL PROPERTIES

Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-(3-(4-fluorophenyl)-3(S)-hydroxypropyl)-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is C_{24}H_{21}F_{2}NO_{3}. Its molecular weight is 409.4 and its structural formula is:

![Ezetimibe Structure](image)

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature.

3.1.3.2 CLINICAL PHARMACOLOGY

Mechanism of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, Ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols.

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of statins and of fenofibrate.

Pharmacodynamics

Clinical studies have demonstrated that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and...
inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Ezetimibe reduces total-C, LDL-C, Apo B, non-HDL-C, and TG, and increases HDL-C in patients with hyperlipidemia. Administration of Ezetimibe with a statin is effective in improving serum total-C, LDL-C, Apo B, non-HDL-C, TG, and HDL-C beyond either treatment alone. Administration of Ezetimibe with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia as compared to either treatment alone. The effects of ezetimibe given either alone or in addition to a statin or fenofibrate on cardiovascular morbidity and mortality have not been established.

**Pharmacokinetics**

*Absorption*

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of Ezetimibe to fasted adults, mean ezetimibe peak plasma concentrations (Cmax) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (Tmax). Ezetimibe-glucuronide mean Cmax values of 45 to 71 ng/mL were achieved between 1 and 2 hours (Tmax). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as Ezetimibe 10-mg tablets. The Cmax value of ezetimibe was increased by 38% with consumption of high-fat meals. Ezetimibe can be administered with or without food.

*Distribution*

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins

*Metabolism*

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

*Excretion*

Following oral administration of $^{14}$C ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10 day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

**Special Populations**

*Pregnancy*
There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 × the human exposure at 10 mg daily based on AUC0–24hr for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 × the human exposure at 10 mg daily based on AUC0–24hr for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

**Nursing Mothers**

It is not known whether ezetimibe is excreted into human breast milk. In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. Because many drugs are excreted in human milk, caution should be exercised when Ezetimibe is administered to a nursing woman. Ezetimibe should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

**Pediatric Use**

The effects of Ezetimibe co-administered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). In a multicenter, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% multi-racial) with HeFH were randomized to receive either Ezetimibe co-administered with simvastatin or simvastatin monotherapy. Inclusion in the study required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161–351 mg/dL) in the Ezetimibe co-administered with simvastatin group compared to 219 mg/dL (range: 149–336 mg/dL) in the simvastatin monotherapy group. The patients received co-administered Ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, co-administered Ezetimibe and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label co-administered Ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

**Geriatric Use**

Monotherapy Studies: of the 2396 patients who received Ezetimibe in clinical studies, 669 (28%) were 65 and older, and 111 (5%) were 75 and older.

Statin Co-Administration Studies: of the 11,308 patients who received Ezetimibe + statin in clinical studies, 3587 (32%) were 65 and older, and 924 (8%) were 75 and older.

No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not
identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment
When used as monotherapy, no dosage adjustment of Ezetimibe is necessary. In the Study of Heart and Renal Protection (SHARP) trial of 9270 patients with moderate to severe renal impairment (6247 non-dialysis patients with median serum creatinine 2.5 mg/dL and median estimated glomerular filtration rate 25.6 mL/min/1.73 m², and 3023 dialysis patients), the incidence of serious adverse events, adverse events leading to discontinuation of study treatment, or adverse events of special interest (musculoskeletal adverse events, liver enzyme abnormalities, incident cancer) was similar between patients ever assigned to ezetimibe 10 mg plus simvastatin 20 mg (n=4650) or placebo (n=4620) during a median follow-up of 4.9 years. However, because renal impairment is a risk factor for statin-associated myopathy, doses of simvastatin exceeding 20 mg should be used with caution and close monitoring when administered concomitantly with Ezetimibe in patients with moderate to severe renal impairment.

Hepatic Impairment
Ezetimibe is not recommended in patients with moderate to severe hepatic impairment. Ezetimibe given concomitantly with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations of hepatic transaminase levels.

3.1.3.3 INDICATIONS AND USAGE

Primary hypercholesterolaemia
Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

Homozgyous Familial Hypercholesterolaemia (HoFH)
Ezetimibe co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozgyous sitosterolaemia (phytosterolaemia)
Ezetimibe is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.
A beneficial effect of Ezetrol on cardiovascular morbidity and mortality has not yet been demonstrated.

3.1.3.4 CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients. When Ezetamibe is co-administered with a statin, please refer to the SPC for that particular medicinal product. Therapy with Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation. Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.
3.1.3.5 WARNINGS

Liver enzymes
In controlled co-administration trials in patients receiving Ezetamibe with a statin, consecutive transaminase elevations (≥ 3 X the upper limit of normal [ULN]) have been observed. When Ezetamibe is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin.

Skeletal muscle
In post-marketing experience with Ezetamibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with Ezetamibe. However, rhabdomyolysis has been reported very rarely with Ezetamibe monotherapy and very rarely with the addition of Ezetamibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level>10 times the ULN, Ezetamibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with Ezetamibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Hepatic insufficiency
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Ezetamibe is not recommended.

Paediatric (10 to 17 Years of Age) Patients
Efficacy and safety of Ezetrol co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche.
In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period> 33 weeks on growth and sexual maturation have not been studied.
The safety and efficacy of Ezetrol co-administered with doses simvastatin above 40mg daily have not been studied in paediatric patients 10 to 17 years of age.
Ezetrol has not been studied in patients younger than 10 years of age or in pre-menarchal girls.
The long-term efficacy of therapy with Ezetrol in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates
The safety and efficacy of Ezetamibe administered with fibrates have not been established. If cholelithiasis is suspected in a patient receiving Ezetamibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.

Ciclosporin
Caution should be exercised when initiating Ezetamibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetamibe and ciclosporin.

Anticoagulants
If Ezetamibe is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.

Excipient
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Pregnancy:**
Ezetamibe should be given to pregnant women only if clearly necessary. No clinical data are available on the use of Ezetamibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofetal development, birth or postnatal development.

**Lactation:**
Ezetamibe should not be used during lactation. Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

3.1.3.6 DRUG INTERACTIONS

**Cyclosporine**
Caution should be exercised when using Ezetimibe and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving Ezetimibe and cyclosporine.

The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe.

**Fibrates**
The efficacy and safety of co-administration of ezetimibe with fibrates other than fenofibrate have not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Co-administration of Ezetimibe with fibrates other than fenofibrate is not recommended until use in patients is adequately studied.

**Fenofibrate**
If cholelithiasis is suspected in a patient receiving Ezetimibe and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered.

**Cholestyramine**
Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

**Coumarin Anticoagulants**
If ezetimibe is added to warfarin, a coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored.

3.1.3.7 DOSAGE FORMS
Ezetimibe Tablets 10 mg
3.2 EXCIPIENTS PROFILE

3.2.1 Methacrylic Acid Copolymers

3.2.1.1 Eudragit EPO

\[
\begin{align*}
R_1, R_3 &= \text{CH}_3 \\
R_2 &= \text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2 \\
R_4 &= \text{CH}_3, \text{C}_4\text{H}_9
\end{align*}
\]

**Chemical Name:** Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1

**CAS number:** 24938-16-7

**Molecular weight:** ≥100 000

**Functional category:** Film former; tablet binder; tablet diluent.

**Application:** Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. *Eudragit E* is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L* and *S* types are used as enteric coating agents since they are resistant to gastric fluid. Different types are available which are soluble at different pH values, e.g., *Eudragit L 100* is soluble at > pH 6, *Eudragit S 100* is soluble at > pH 7. Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5-20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10-50%.

**Description:** *Eudragit E* is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to approximately pH 5). *Eudragit EPO* is available as a solvent-free granules contain 98% dried weight content of *Eudragit E*.

**Typical Properties**

- **Alkali value:** 162-198
- **Density (bulk):** 0.390 g/cm³
- **Density (tapped):** 0.424 g/cm³
- **Density (true):** 0.811-0.821 g/cm³
- **Refractive index:** n_D^20 = 1.38-1.385
- **Viscosity (dynamic):** 3-12 mPa s

**Regulatory Status:** Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

**Pharmacopoeial Status:** USP
3.2.1.2 *Eudragit S100*

**Chemical Name:** Poly(methacrylic acid, methyl methacrylate) 1:2  
**CAS number:** 25086-15-1  
**Molecular weight:** ≥100 000  
**Functional category:** Film former; tablet binder; tablet diluent.  
**Application:** *Eudragit S100* types are used as enteric coating agents since they are resistant to gastric fluid. *Eudragit S100* is soluble at > pH 7.  
**Description:** *Eudragit S100* is anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:2 in *Eudragit S100*. Polymers are readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus affording film coats which are resistant to gastric media but soluble in intestinal fluid. *Eudragit S100* are white free-flowing powders with at least 95% of dry polymers.  
**Typical Properties**  
*Acid value:* 180-200  
*Density (bulk):* 0.390 g/cm³  
*Density (tapped):* 0.424 g/cm³  
*Density (true):* 0.831-0.852 g/cm³  
*Refractive index:* $n_D^{20} = 1.39-1.395$  
*Viscosity (dynamic):* 50-200 mPa s  
**Regulatory Status:** Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.  
**Pharmacopoeial Status:** USP
3.2.1.3 *Eudragit L100*

\[ \text{R}_1, \text{R}_3 = \text{CH}_3 \\
\text{R}_2 = \text{H} \\
\text{R}_4 = \text{CH}_3 \]

**Chemical Name:** Poly(methacrylic acid, methyl methacrylate) 1:1  
**CAS number:** 25806-15-1  
**Molecular weight:** \( \geq 100,000 \)

**Functional category:** Film former; tablet binder; tablet diluent.  
**Application:** *Eudragit L100* is used as enteric coating agents since it is resistant to gastric fluid. *Eudragit L100* is soluble at > pH 6.  
**Description:** *Eudragit L100* is anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in *Eudragit L100*. Polymers are readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus affording film coats which are resistant to gastric media but soluble in intestinal fluid. *Eudragit L100* is white free-flowing powders with at least 95% of dry polymers.

**Typical Properties**  
**Acid value:** 300-330  
**Density (bulk):** 0.390 g/cm\(^3\)  
**Density (tapped):** 0.424 g/cm\(^3\)  
**Density (true):** 0.831-0.852 g/cm\(^3\)  
**Refractive index:** \( n_D^{20} = 1.387-1.392 \)  
**Viscosity (dynamic):** 100-200 mPa s

**Regulatory Status:** Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.  
**Pharmacopoeial Status:** USP
3.2.1.4 Eudragit RSPO

\[\begin{align*}
R_1 &= H, \text{CH}_3 \\
R_2 &= \text{CH}_3, \text{C}_2\text{H}_5 \\
R_3 &= \text{CH}_3 \\
R_4 &= \text{CH}_2\text{CH}_2\text{N(CH}_3)_3^+\text{Cl}^- \\
\end{align*}\]

**Chemical Name:** Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1

**CAS number:** 33434-24-1

**Molecular weight:** $\geq 100,000$

**Functional category:** Film former; tablet binder; tablet diluent.

**Application:** Eudragit RSPO is used to form water-insoluble film coats for sustained-release products and by mixing with Eudragit RLPO together films of varying permeability can be obtained.

**Description:** Eudragit RS is copolymers synthesized from acrylic acid and methacrylic acid esters with having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Polymers are water-insoluble, and films prepared from Eudragit RSPO is only slightly permeable to water. Eudragit RS PO is fine, white powders with a slight amine-like odor and contain $\geq 97\%$ of dry polymer.

**Typical Properties**

- **Alkali value:** 12.1-18.3
- **Density (bulk):** 0.390 g/cm$^3$
- **Density (tapped):** 0.424 g/cm$^3$
- **Density (true):** 0.816-0.836 g/cm$^3$
- **Refractive index:** $n_D^{20} = 1.38-1.385$
- **Viscosity (dynamic):** $\leq 15$ mPa s

**Regulatory Status:** Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

**Pharmacopoeial Status:** USP
### 3.2.1.5 Eudragit RLPO

![Chemical Structure of Eudragit RLPO](image)

\[ R_1 = \text{H}, \text{CH}_3 \]
\[ R_2 = \text{CH}_3, \text{C}_2\text{H}_5 \]
\[ R_3 = \text{CH}_3 \]
\[ R_4 = \text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_3\text{Cl}^- \]

**Chemical Name**: Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethy methacrylate chloride) 1:2:0.2

**CAS number**: 33434-24-1

**Molecular weight**: ≥100 000

**Functional category**: Film former; tablet binder; tablet diluent.

**Application**: Eudragit RSPO is used to form water-insoluble film coats for sustained-release products and by mixing with Eudragit RLPO together films of varying permeability can be obtained.

**Description**: Eudragit RS is copolymers synthesized from acrylic acid and methacrylic acid esters with having 10% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Polymers are water-insoluble, and films prepared from Eudragit RSPO is only slightly permeable to water. Eudragit RS PO is fine, white powders with a slight amine-like odor and contain ≥ 97% of dry polymer.

**Typical Properties**

- **Alkali value**: 23.9-32.3
- **Density (bulk)**: 0.390 g/cm³
- **Density (tapped)**: 0.424 g/cm³
- **Density (true)**: 0.816-0.836 g/cm³
- **Refractive index**: \( n_D^{20} = 1.38-1.385 \)
- **Viscosity (dynamic)**: ≤15 mPa s

**Regulatory Status**: Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

**Pharmacopoeial Status**: USP
3.2.2 Hydrophilic Polymers

3.2.2.1 Polyvinyl Alcohol

**Chemical name:** Ethenol, homopolymer

**CAS number:** 9002-89-5

**Empirical formula:** \((C_2H_4O)_n\)

**Molecular weight:** 30 000-200 000

Polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula \((C_2H_4O)_n\). The value of \(n\) for commercially available materials lies between 500-5000, equivalent to a molecular weight range of approximately 30 000 to 200 000.

**Structural formula:**

\[
\begin{array}{c}
\text{CH}_2 \text{CH} \\
\text{OH}
\end{array}
\]

**Functional category:** Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

**Applications:** Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations. It is used (0.25-3.0%) as a stabilizing agent for emulsions. Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration, and in transdermal patches. Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsions</td>
<td>0.5</td>
</tr>
<tr>
<td>Ophthalmic formulations</td>
<td>0.25-3.0</td>
</tr>
<tr>
<td>Topical lotions</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Description:** Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

**Typical Properties**

- **Melting point:** 228°C for fully hydrolyzed grades; 180-190°C for partially hydrolyzed grades.
- **Refractive index:** \(n_D^{25} = 1.49-1.53\)
- **Solubility:** soluble in water; insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90°C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature.
- **Specific gravity:** 1.19-1.31 for solid at 25°C, 1.02 for 10% w/v aqueous solution at 25°C.
- **Specific heat:** 1.67 J/g (0.4 cal/g)
3.2.2.2 Povidone

**Synonyms**: Kollidon, Polyvidone, polyvinylpyrrolidone, Plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], PVP; 1-vinyl-2-pyrrolidinone polymer.

**Chemical Name**: 1-Ethenyl-2-pyrrolidinone homopolymer

**CAS Number**: 9003-39-8

**Empirical Formula**: \((C_6H_9NO)_n\)

**Molecular Weight**: (K30) 50000

The USP describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. The K-value is calculated using Fikentscher’s equation shown below:

\[
\log z = c \left( \frac{75 k^2}{1 + 1.5 kc} \right) + k
\]

where \(z\) is the relative viscosity of the solution of concentration \(c\), \(k\) is the K-value \(\times 10^{-3}\), and \(c\) is the concentration in % w/v.

Alternatively, the K-value may be determined from the following equation:

\[
K\text{-value} = \sqrt{\frac{300 c \log z + (c + 1.5 c \log z) + 1.5}{0.15c + 0.003c^3}}
\]

where \(z\) is the relative viscosity of the solution of concentration \(c\), \(k\) is the K-value \(\times 10^{-3}\), and \(c\) is the concentration in % w/v.

**Structural Formula**:

\[
\begin{align*}
\text{CH}_{2} & \quad \text{O} \\
\text{CH} & \quad \text{NH} \\
\text{C} & \quad \text{C}
\end{align*}
\]

**Functional Category**: Disintegrant; dissolution aid; suspending agent; tablet binder.

**Application**: Although povidone is used in a variety of pharmaceutical formulations it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a disintegrant and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. Special grades of pyrogen-free povidone are available and have been used in parenteral formulations.

**Description**: Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30...
are manufactured by spray-drying and exist as spheres. Povidone K-90 and higher
K-value povidones are manufactured by drum drying and exist as plates.

**Typical Properties:**

*Acidity/alkalinity:* $\text{pH} = 3.0-7.0$ (5% w/v aqueous solution)

*Density (bulk):* 0.409 g/cm$^3$\(^{(b)}\)

*Density (tapped):* 0.508 g/cm$^3$\(^{(b)}\)

*Density (true):* 1.180 g/cm$^3$\(^{(b)}\)

*Flowability:* 16 g/s for povidone K-29/32.

*Hygroscopicity:* povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

*Melting point:* softens at 150°C

*Solubility:* freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water the concentration of a solution is limited only by the viscosity of the resulting solution which is a function of the K-value.
3.2.2.3 **Poloxamer**

**Synonyms:** Lutrol; Monolan, Pluronic, poloxalkol, polyethylene-propylene glycol copolymer, polyoxyethylene-polyoxypropylene copolymer, Supronic, Synperonic.

**Chemical Name:** $\alpha$-Hydro-$\omega$-hydroxypropoxy (oxyethylene) poly (oxypropylene) poly (oxyethylene) block copolymer.

**CAS Number:** 9003-11-6

**Empirical Formula & Molecular Weight:** The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula:

$$\text{HO(C}_2\text{H}_4\text{O})_a(C}_3\text{H}_6\text{O})_b(C}_2\text{H}_4\text{O})_a\text{H}$$

<table>
<thead>
<tr>
<th>Poloxamer</th>
<th>Physical form</th>
<th>a</th>
<th>b</th>
<th>Average molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>407</td>
<td>Solid</td>
<td>101</td>
<td>56</td>
<td>9840-14 600</td>
</tr>
</tbody>
</table>

**Functional Category:** Dispersing agent; emulsifying and co-emulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

**Application:** Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available.

Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents, in ointments, suppository bases, gels, and as tablet binders and coatings. Poloxamer 407 are used in solutions for contact lens care.

**Description:** Poloxamers generally occur as white-colored, waxy, free flowing prilled granules, or as cast solids. They are practically odorless and tasteless.

**Typical Properties:**

- **Acidity/alkalinity:** $\text{pH} = 5.0-7.4$ for a 2.5% w/v aqueous solution.
- **Density:** 1.06 g/cm$^3$ at 25°C
- **Flash point:** 260°C
- **Flowability:** solid poloxamers are free flowing.
- **Melting point:** 52-57°C for poloxamer 407.
- **Moisture content:** poloxamers generally contain less than 0.5% w/w water and are hygroscopic only at greater than 80% relative humidity.
- **Viscosity (dynamic):** 1000 mPa s (1000 cP) as a melt at 77°C.
3.2.2.4 Polyethylene Glycol

**Synonyms:** Breox PEG; Carbowax; Hodag PEG; Lutrol E; PEG; polyoxyethylene glycol.

**Chemical Name:** $\alpha$-Hydro-\(\omega\)-hydroxy-poly(oxy-1,2-ethanediyl)

**CAS Number:** 25322-68-3

**Empirical Formula & Molecular Weight:**

\[
HOCH_2(CH_2OCH_2)_mCH_2OH
\]

Where \(m\) represents the average number of oxyethylene groups. Alternatively, the general formula \(H(OCH_2CH_2)_nOH\) may be used to represent polyethylene glycol, where \(n\) is a number one more than the value of \(m\) in the previous formula.

<table>
<thead>
<tr>
<th>Grade</th>
<th>M</th>
<th>Average molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 3000</td>
<td>60-75</td>
<td>2700-3300</td>
</tr>
<tr>
<td>PEG 3350</td>
<td>75.7</td>
<td>3000-3700</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>69-84</td>
<td>3000-4800</td>
</tr>
<tr>
<td>PEG 4600</td>
<td>104.1</td>
<td>4400-4800</td>
</tr>
<tr>
<td>PEG 8000</td>
<td>181.4</td>
<td>7000-9000</td>
</tr>
</tbody>
</table>

**Structural Formula:**

\[
\text{HO} - \left( \text{CH}_2\text{O} \right)_\text{m} - \text{CH}_2\text{OH}
\]

**Molecular Weight:** Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

**Application:** Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin, see Section 14. Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases. Solid grades are generally employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol. Mixtures of polyethylene glycols can be used as suppository bases where they have the following advantages over fats: the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; physical stability on storage is better; suppositories are readily miscible with rectal fluids. Disadvantages of using polyethylene glycols are: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.
In solid-dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, a mixture of the powdered constituents with 10-15% w/w PEG 6000 is heated to 70-75°C. The mass becomes paste-like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers. The presence of polyethylene glycols, especially liquid grades, in film coats tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of over-heating.

In addition, polyethylene glycols have been used in the preparation of urethane hydrogels which are used as controlled-release agents.

Description: The USP describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight, but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG >1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

Typical Properties:
Density: 1.15-1.21 g/cm³ at 25°C for solid PEGs.
Melting point: 55-63°C for PEG 6000;
Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight.
Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol, and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.
Surface tension: approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.
3.2.2.5 Hydroxypropyl Cellulose

**Synonymes:** Cellulose, hydroxypropyl ether; E463; hyprollose; Klucel; Methocel; Nisso HPC; oxypropylated cellulose.

**Chemical Name:** Cellulose, 2-hydroxypropyl ether

**CAS Number:** 9004-64-2

**Empirical Formula & Molecular Weight:**
The USP describes hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or some other suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades which have different solution viscosities. Molecular weight ranges from 50 000-1 250 000

**Structural Formula:**

![Structural Formula](image)

Where R is H or \([-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}]_n\)

**Functional Category:** Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

**Application:** Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended release-matrix former. Concentrations of between 2-6% w/w of hydroxypropyl cellulose may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of between 15-35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the hydroxypropyl cellulose viscosity and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Either aqueous solutions, containing hydroxypropyl cellulose along with some methylcellulose, or ethanolic solutions may be used. Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant, Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

**Description:** Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

**Typical Properties:**

- **Acidity/alkalinity:** pH = 5.0-8.5 for a 1% w/v aqueous solution.
- **Density (bulk):** 0.5 g/cm³
- **Interfacial tension:** 12.5 mN/m for a 0.1% w/v aqueous solution vs. mineral oil.
- **Melting point:** softens at 130°C; chars at 260-275°C.
- **Moisture content:** hydroxypropyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content, and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are: 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity.
- **Refractive index:** \(n_D^{20} = 1.3353\) for a 2% w/v aqueous solution.
Solubility: soluble 1 in 10 parts dichloromethane, 1 in 2.5 parts ethanol, 1 in 2 parts methanol, 1 in 5 parts propan-2-ol, 1 in 5 parts propylene glycol, and 1 in 2 parts water; practically insoluble in aliphatic hydrocarbons, aromatic hydrocarbons, carbon tetrachloride, petroleum distillates, glycerin, and oils. Hydroxypropyl cellulose is freely soluble in water below 38°C forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40-45°C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as: dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol; methanol; propan-2-ol (95%); and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids which are borderline solvents, such as: acetone; butyl acetate; cyclohexanol; dichloromethane; lactic acid; methylacetate; methylethyl ketone; propan-2-ol (99%); and tert-butanol. The higher viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5-15%) of a cosolvent. For example, dichloromethane is a borderline solvent for Klucel HF and solutions have a granular texture, but by adding 10% methanol a smooth solution may be produced.

Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.
3.2.2.6 Hydroxypropyl methylcellulose

Synonyms: Benecel MHPC; Cellulose, hydroxypropyl methyl ether; E464; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose.

Chemical Name: Cellulose, 2-Hydroxypropyl methyl ether

CAS Number: 9004-65-3

Empirical Formula & Molecular Weight:
The PhEur describes hydroxypropyl methylcellulose as a partly \( O \)-methylated and \( O \)-(2-hydroxypropylated) cellulose. Hydroxypropyl methylcellulose defined in the USP specifies the substitution type by appending a four digit number to the nonproprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH\(_3\)). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH\(_2\)CHOHCH\(_3\)), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

Structural Formula:

Where R is H, CH\(_3\), or [CH\(_3\)CH(OH)CH\(_2\)].

Functional Category: Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Application: Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations. In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder, in film-coating, and as an extended-release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10-80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations between 2-20% w/w are used as film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents. Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hydroxypropyl methylcellulose is used in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description: Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Typical Properties:
Acidity/alkalinity: pH = 5.5-8.0 for a 1% w/w aqueous solution.
Ash: 1.5-3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (bulk): 0.341 g/cm³
Density (tapped): 0.557 g/cm³
Density (true): 1.326 g/cm³
Melting point: browns at 190-200°C; chars at 225-230°C.
Glass transition temperature: 170-180°C.
Moisture content: hydroxypropyl methylcellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.
Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hydroxypropyl methylcellulose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.
Specific gravity: 1.26
Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared although hydroxypropyl methylcellulose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hydroxypropyl methylcellulose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

To prepare an aqueous solution, it is recommended that hydroxypropyl methylcellulose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90°C then the remaining hydroxypropyl methylcellulose added. Cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hydroxypropyl methylcellulose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to 1 part of hydroxypropyl methylcellulose. Cold water is then added to produce the required volume.
3.2.3 Superdisintegrants

3.2.3.1 Sodium Starch Glycolate

**Synonyms:** Carboxymethyl starch, sodium salt; *Explotab*; *Primojel*.
**Chemical Name:** Sodium carboxymethyl starch
**CAS Number:** 9063-38-1

**Empirical Formula & Molecular Weight:**
The USP states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. The molecular weight is typically 500000-1000000. The PhEur describes two types of material; Type A, equivalent to the USP material, containing 2.8-4.2% of sodium and Type B containing 2.0-3.4% of sodium. Sodium starch glycolate may be characterized by the degree of substitution and crosslinking.

**Structural Formula:**

![Structural Formula of Sodium Starch Glycolate]

**Functional Category:** Tablet and capsule disintegrant.
**Application:** Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

**Description:** Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30-100 μm in diameter with some less-spherical granules ranging from 10-35 μm in diameter.

**Typical Properties:**
- **Acidity/alkalinity:** pH = 3.0-5.0% or, pH = 5.5-7.5% for a 3.3% aqueous dispersion.
- **Ash:** ≤15%
- **Density (bulk):** 0.756 g/cm³
- **Density (tapped):** 0.945 g/cm³
- **Density (true):** 1.443 g/cm³
- **Melting point:** does not melt, but chars at approximately 200°C.
- **Particle size distribution:** 100% of particles less than 104 μm in size. Average particle size is 42 μm for *Explotab*.
- **Solubility:** sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v it disperses in cold water and settles in the form of a highly hydrated layer.
- **Specific surface area:** 0.24 m²/g
- **Swelling capacity:** in water, sodium starch glycolate swells up to 300 times its volume.
- **Viscosity (dynamic):** ≤200 mPa s (200 cP) for a 4% w/v aqueous dispersion. Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.
3.2.3.2 Croscarmellose Cellulose

**Synonyms:** Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab.

**Chemical Name:** Cellulose, carboxymethyl ether, sodium salt, crosslinked

**CAS Number:** 74811-65-7

**Empirical Formula:** Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

**Structural Formula:**

![Structural formula of croscarmellose sodium]

**Functional Category:** Tablet and capsule disintegrant.

**Application:** Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations the croscarmellose sodium is best added in both the wet and dry stages of the process (intra- and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Concentrations of up to 5% w/w of croscarmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

**Description:** Croscarmellose sodium occurs as an odorless, white-colored powder.

**Typical Properties:**
- Bonding index: 0.0456
- Brittle fracture index: 0.1000
- Compression pressure: 20 kN/cm²
- Permanent deformation pressure: 29.9 kN/cm²
- Reduced modulus of elasticity: 960
- Tensile strength: 1.3605 kN/cm²
- Density (bulk): 0.529 g/cm³ for Ac-Di-Sol®
- Density (tapped): 0.819 g/cm³ for Ac-Di-Sol®
- Density (true): 1.543 g/cm³ for Ac-Di-Sol®
- Solubility: insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water.
- Specific surface area: 0.81-0.83 m²/g
3.2.3.3 Crospovidone

**Synonyms:** Cross-linked povidone; Kollidon CL; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolyvinylpyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

**Chemical Name:** 1-Ethenyl-2-pyrrolidinone homopolymer

**CAS Number:** 9003-39-8

**Empirical Formula:** \((\text{C}_6\text{H}_9\text{NO})_n\)

**Molecular Weight:** > 1000000

Crospovidone is a water-insoluble synthetic crosslinked homopolymer of \(N\)-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

**Functional Category:** Tablet disintegrant.

**Application:** Crospovidone is a water-insoluble tablet disintegrant used at 2-5% concentration in tablets prepared by direct compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels.

**Description:** Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

**Typical Properties:**
- **Acidity/alkalinity:** \(\text{pH} = 5.0-8.0\) (1% w/v aqueous slurry)
- **Compression pressure:** 20.39 kN/cm\(^2\)
- **Tensile strength:** 0.7471 kN/cm\(^2\)
- **Permanent deformation pressure:** 140.4 kN/cm\(^2\)
- **Brittle fracture index:** 0.2371
- **Bonding index:** 0.0053
- **Reduced modulus of elasticity:** 10621
- **Density:** 1.22 g/cm\(^3\)
- **Density (bulk):** 0.363 g/cm\(^3\)
- **Density (tapped):** 0.534 g/cm\(^3\)
- **Moisture content:** Maximum moisture sorption is approximately 60%.
- **Solubility:** Practically insoluble in water and most common organic solvents.
- **Specific surface area:** 0.77-0.82 m\(^2\)/g (BET method).

**Structural Formula:**

```
\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{H} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]
```
### 3.3 LIST OF INSTRUMENTS

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Instrument</th>
<th>Model</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fourier transformed infrared spectroscopy</td>
<td>FTIR 8300</td>
<td>Shimadzu, Japan</td>
</tr>
<tr>
<td>2</td>
<td>Differential scanning calorimetry</td>
<td>DSC 60</td>
<td>Shimadzu, Japan</td>
</tr>
<tr>
<td>3</td>
<td>X-ray powder diffractometry</td>
<td>PW 1710</td>
<td>Philips, Holand</td>
</tr>
<tr>
<td>4</td>
<td>Scanning electron microscopy</td>
<td>JSM 50A</td>
<td>JEOL, Japan</td>
</tr>
<tr>
<td>5</td>
<td>pH meter</td>
<td>LI 613</td>
<td>Elico, India</td>
</tr>
<tr>
<td>6</td>
<td>Sonicator</td>
<td>-</td>
<td>PCI, India</td>
</tr>
<tr>
<td>7</td>
<td>Tablet punching machine</td>
<td>Single rotary, 8 station</td>
<td>CIP instruments, India</td>
</tr>
<tr>
<td>8</td>
<td>Tablet dissolution tester</td>
<td>Disso 2000</td>
<td>Labindia, India</td>
</tr>
<tr>
<td>9</td>
<td>Tablet disintegration tester</td>
<td>-</td>
<td>Lab Hosp, India</td>
</tr>
<tr>
<td>10</td>
<td>Hardness tester</td>
<td>-</td>
<td>Rajesh chemicals, India</td>
</tr>
<tr>
<td>11</td>
<td>Friability tester</td>
<td>-</td>
<td>Electro Lab, India</td>
</tr>
<tr>
<td>12</td>
<td>Stability chamber</td>
<td>EC 2054</td>
<td>HMG India</td>
</tr>
<tr>
<td>13</td>
<td>UV- Visible spectrophotometer</td>
<td>Pharmaspec 1700</td>
<td>Shimadzu, Japan</td>
</tr>
<tr>
<td>14</td>
<td>HPLC</td>
<td>PU-2080; UV-2075</td>
<td>Jasco, Japan</td>
</tr>
<tr>
<td>15</td>
<td>Optical microscope</td>
<td>VJ2 BIK</td>
<td>Labo, India</td>
</tr>
<tr>
<td>16</td>
<td>Refrigeration Centrifuge</td>
<td>RC4100 D</td>
<td>Eitek, India</td>
</tr>
<tr>
<td>17</td>
<td>Micro-centrifuge</td>
<td>Spinwin 1.5 ml</td>
<td>Bio Era, India</td>
</tr>
<tr>
<td>18</td>
<td>Weighing balance</td>
<td>HR 200</td>
<td>AND, India</td>
</tr>
<tr>
<td>19</td>
<td>Overhead Stirrer</td>
<td>Remi stirrer</td>
<td>Remi , Mumbai</td>
</tr>
<tr>
<td>20</td>
<td>Water bath</td>
<td>Dolphin Instrument</td>
<td>Dolphin</td>
</tr>
<tr>
<td>21</td>
<td>Hot air oven</td>
<td>Dolphin Model 1033</td>
<td>Dolphin</td>
</tr>
<tr>
<td>22</td>
<td>Vacuum filtration assembly</td>
<td>-</td>
<td>Prashant Industries Pune</td>
</tr>
<tr>
<td>23</td>
<td>Sieve shaker</td>
<td>-</td>
<td>Dolphin</td>
</tr>
<tr>
<td>24</td>
<td>Tap density apparatus</td>
<td>-</td>
<td>Dolphin</td>
</tr>
</tbody>
</table>
### 3.4 LIST CHEMICALS & REAGENTS

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Chemicals &amp; Reagents</th>
<th>Source/ Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disodium hydrogen phosphate</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>2</td>
<td>Potassium dihydrogen phosphate</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>3</td>
<td>Glacial Acetic acid</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>4</td>
<td>Hydrochloric acid</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>5</td>
<td>Sodium hydroxide</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>6</td>
<td>Sodium chloride</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>7</td>
<td>Methanol</td>
<td>Rankem chemicals</td>
</tr>
<tr>
<td>8</td>
<td>Dichloromethane</td>
<td>Rankem chemicals</td>
</tr>
<tr>
<td>9</td>
<td>Acetonitrile</td>
<td>Rankem chemicals</td>
</tr>
<tr>
<td>10</td>
<td>Ethanol</td>
<td>Rankem chemicals</td>
</tr>
<tr>
<td>11</td>
<td>HPLC grade water</td>
<td>Merck Specialties Private Ltd, Mumbai.</td>
</tr>
<tr>
<td>12</td>
<td>Chloroform</td>
<td>Merck Specialties Private Ltd, Mumbai.</td>
</tr>
<tr>
<td>13</td>
<td>Sodium acetate</td>
<td>Loba chemicals</td>
</tr>
</tbody>
</table>

### 3.5 LIST OF API & EXCIPIENTS

<table>
<thead>
<tr>
<th>S. No.</th>
<th>API &amp; Excipients</th>
<th>Source/ Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atorvastatin Calcium</td>
<td>MSN Pharmachem Pvt. Ltd.</td>
</tr>
<tr>
<td>2</td>
<td>Fenofibrate</td>
<td>Alembic Ltd.</td>
</tr>
<tr>
<td>3</td>
<td>Ezetimibe</td>
<td>Inogent Laboratories Pvt. Ltd.</td>
</tr>
<tr>
<td>4</td>
<td>Eudragit® S100</td>
<td>Evonic India Ltd.</td>
</tr>
<tr>
<td>5</td>
<td>Eudragit® L100</td>
<td>Evonic India Ltd.</td>
</tr>
<tr>
<td>6</td>
<td>Eudragit® EPO</td>
<td>Evonic India Ltd.</td>
</tr>
<tr>
<td>7</td>
<td>Eudragit® RSPO</td>
<td>Evonic India Ltd.</td>
</tr>
<tr>
<td>8</td>
<td>Eudragit® RLPO</td>
<td>Evonic India Ltd.</td>
</tr>
<tr>
<td>9</td>
<td>Hydroxypropyl methylcellulose</td>
<td>Colorcon Asia Ltd.</td>
</tr>
<tr>
<td>10</td>
<td>Hydroxypropyl cellulose</td>
<td>ShinShu Chemicals</td>
</tr>
<tr>
<td>11</td>
<td>Povidone</td>
<td>BASF Ltd.</td>
</tr>
<tr>
<td>12</td>
<td>Propylene glycol</td>
<td>BASF Ltd.</td>
</tr>
<tr>
<td></td>
<td>Material</td>
<td>Supplier</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>13</td>
<td>Poloxamer</td>
<td>BASF Ltd.</td>
</tr>
<tr>
<td>14</td>
<td>Polyvinyl alcohol</td>
<td>BASF Ltd.</td>
</tr>
<tr>
<td>15</td>
<td>Croscarmellose sodium</td>
<td>FMC Biopolymer</td>
</tr>
<tr>
<td>16</td>
<td>Sodium starch glycolate</td>
<td>DMV International Ltd.</td>
</tr>
<tr>
<td>17</td>
<td>Crospovidone</td>
<td>Roquette Ltd.</td>
</tr>
<tr>
<td>18</td>
<td>Calcium sulphate dihydrate</td>
<td>JRS Pharma Ltd.</td>
</tr>
<tr>
<td>19</td>
<td>Xanthan gum</td>
<td>CP kelco Ltd.</td>
</tr>
<tr>
<td>20</td>
<td>Hydroxyethyl cellulose</td>
<td>Aqualone Ltd.</td>
</tr>
<tr>
<td>21</td>
<td>Sodium carboxymethyl cellulose</td>
<td>CP kelco Ltd.</td>
</tr>
<tr>
<td>22</td>
<td>Sodium bicarbonate</td>
<td>Canton Ltd.</td>
</tr>
<tr>
<td>23</td>
<td>Citric acid anhydrous</td>
<td>Canton Ltd.</td>
</tr>
<tr>
<td>24</td>
<td>Avicel® PH 200</td>
<td>FMC Biopolymer</td>
</tr>
<tr>
<td>25</td>
<td>Magnesium Stearate</td>
<td>Loba Chemical</td>
</tr>
<tr>
<td>26</td>
<td>Pearlitol® Flash</td>
<td>Roquette Ltd.</td>
</tr>
<tr>
<td>27</td>
<td>Heavy Magnesium oxide DC</td>
<td>Loba chemicals</td>
</tr>
<tr>
<td>28</td>
<td>Aspartame</td>
<td>Nutrasweet Ltd.</td>
</tr>
<tr>
<td>29</td>
<td>Strawberry Powder Flavor</td>
<td>Ferminich Ltd.</td>
</tr>
</tbody>
</table>
3.6 CERTIFICATE OF ANALYSIS
3.6.1 Atorvastatin Calcium

<table>
<thead>
<tr>
<th>SL. No.</th>
<th>TEST</th>
<th>RESULT</th>
<th>SPECIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Description</td>
<td>Off white colored crystalline powder.</td>
<td>White to off white color crystalline powder.</td>
</tr>
<tr>
<td>2.0</td>
<td>Solubility</td>
<td>Freely soluble in Methanol, Soluble in Dimethyl sulphoxide, Slightly soluble in Ethanol. Very slightly soluble in water and Acetonitrile.</td>
<td>Freely soluble in Methanol, Soluble in Dimethyl sulphoxide, Slightly soluble in Ethanol. Very slightly soluble in water and Acetonitrile.</td>
</tr>
<tr>
<td>3.0</td>
<td>Identification by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>By IR</td>
<td>Matches with working standard</td>
<td>The IR spectrum of the sample should match with that of the working standard.</td>
</tr>
<tr>
<td>3.2</td>
<td>By HPLC</td>
<td>The retention time of the principal peak of Sample matches with that of working standard.</td>
<td>The retention time of the principal peak of Sample should match with that of working standard.</td>
</tr>
<tr>
<td>3.3</td>
<td>Test for Calcium</td>
<td>Positive</td>
<td>To respond to the test for calcium</td>
</tr>
<tr>
<td>4.0</td>
<td>Water content by KF</td>
<td>5.0 w/w</td>
<td>Between 3.5% to 5.5% w/w</td>
</tr>
<tr>
<td>5.0</td>
<td>Calcium Content by titrimetry (On anhydrous basis)</td>
<td>3.4% w/w</td>
<td>Between 3.0% to 3.6% w/w</td>
</tr>
<tr>
<td>6.0</td>
<td>Heavy metals</td>
<td>Less than 10 ppm</td>
<td>Not more than 10 ppm</td>
</tr>
<tr>
<td>7.0</td>
<td>Specific optical rotation (1% sol in DMSO / On Anhydrous basis)</td>
<td>-8.4°</td>
<td>Between -6.8° and -10.0°</td>
</tr>
<tr>
<td>8.0</td>
<td>Related substances by HPLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1</td>
<td>Desfluro Impurity</td>
<td>0.01%</td>
<td>Not more than 0.15 %</td>
</tr>
<tr>
<td>8.2</td>
<td>Lactone Impurity</td>
<td>0.02%</td>
<td>Not more than 0.15 %</td>
</tr>
<tr>
<td>8.3</td>
<td>Enter Impurity</td>
<td>0.01%</td>
<td>Not more than 0.15 %</td>
</tr>
<tr>
<td>8.4</td>
<td>Major unknown individual impurity</td>
<td>0.04%</td>
<td>Not more than 0.10 %</td>
</tr>
<tr>
<td>8.5</td>
<td>Total impurities</td>
<td>0.13%</td>
<td>Not more than 1.0 %</td>
</tr>
</tbody>
</table>

The product CONFORMS to above specifications.
# Chapter 3: Materials

## MSN Pharmachem Pvt. Ltd.
Factory: Plot no: 212, phase-2, IDA Pushamylaram,
Panchaneru (Mandal), Medak (Dist), Andhra Pradesh-502 307

## CERTIFICATE OF ANALYSIS

<table>
<thead>
<tr>
<th>Product: ATORVASTATIN CALCIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch No.: AC10051208</td>
</tr>
<tr>
<td>Batch Quantity: 25.6 Kgs</td>
</tr>
<tr>
<td>AR No.: FP080406</td>
</tr>
<tr>
<td>Reference: In house</td>
</tr>
<tr>
<td>Mfg. Date: December 2008</td>
</tr>
<tr>
<td>Retest Date: May 2011</td>
</tr>
<tr>
<td>Date of Analysis: 31.12.2008</td>
</tr>
<tr>
<td>Specification No: QC-FPAC1-001/03</td>
</tr>
</tbody>
</table>

### Sl. No. | TEST                              | RESULT  | SPECIFICATION                                      |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9.0</td>
<td>Assay by HPLC</td>
<td>99.3% w/w</td>
<td>Not less than 98.0% and Not more than 102.0% w/w</td>
</tr>
<tr>
<td>10.0</td>
<td>Residual solvents by GC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1</td>
<td>Methanol</td>
<td>Not detected</td>
<td>Not more than 3000 ppm</td>
</tr>
<tr>
<td>10.2</td>
<td>Acetonitrile</td>
<td>Not detected</td>
<td>Not more than 410 ppm</td>
</tr>
<tr>
<td>10.3</td>
<td>Isopropyl Alcohol</td>
<td>Not detected</td>
<td>Not more than 5000 ppm</td>
</tr>
<tr>
<td>10.4</td>
<td>Cyclohexane</td>
<td>29 ppm</td>
<td>Not more than 3880 ppm</td>
</tr>
<tr>
<td>10.5</td>
<td>Toluene</td>
<td>37 ppm</td>
<td>Not more than 890 ppm</td>
</tr>
<tr>
<td>11.0</td>
<td>XRD</td>
<td>Sample X-Ray Diffract gram matches with working standard crystalline form-1</td>
<td>Sample X-Ray Diffractogram should match with working standard crystalline form-1</td>
</tr>
</tbody>
</table>

The product CONFORMS to above specifications.

Compiled by: [Signature]

Checked by: [Signature]

Head, Quality Control: [Signature]
### 3.6.2 Fenofibrate

#### PRODUCT: FENOFIBRATE BP

<table>
<thead>
<tr>
<th>BATCH NO</th>
<th>10017382</th>
<th>A. R. NO</th>
<th>3000052988</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFG</td>
<td>NOV 2006</td>
<td>RETEST</td>
<td>OCT 2010</td>
</tr>
</tbody>
</table>

| BATCH SIZE | 233.1 Kg |

<table>
<thead>
<tr>
<th>SR. NO.</th>
<th>TEST Description</th>
<th>RESULT</th>
<th>SPECIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Characters</td>
<td>Almost white crystalline powder</td>
<td>A white to almost white, crystalline powder. Practically insoluble in water, very soluble in methylene chloride, slightly soluble in alcohol.</td>
</tr>
<tr>
<td></td>
<td>Solubility</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>Identification</td>
<td>81.3°C Comparable</td>
<td>79°C to 82°C I.R. spectrum of a dispersion of sample in KBr is concordant with 2-[(4-Chlorobenzyl) Phenoxy]-2-Methyl Propanoic Acid 1-Methyl Ethyl Ester WS spectrum</td>
</tr>
<tr>
<td></td>
<td>Melting point By I.R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>Appearance of solution (0.5 g sample in 10 ml acetone)</td>
<td>Complies</td>
<td>The solution is clear and not more intensely colored than reference solution BY₆</td>
</tr>
<tr>
<td>04</td>
<td>Acidity (1.0 g sample in 50 ml alcohol)</td>
<td>0.10 ml</td>
<td>Not more than 0.20 ml of 0.1 M sodium hydroxide is required to change the colour of the indicator to pink.</td>
</tr>
<tr>
<td>05</td>
<td>Related substances (HPLC)</td>
<td>Not detected</td>
<td>NMT 0.10 %</td>
</tr>
<tr>
<td></td>
<td>Impurity A</td>
<td>0.01 %</td>
<td>NMT 0.10 %</td>
</tr>
<tr>
<td></td>
<td>Impurity B</td>
<td>Not detected</td>
<td>NMT 0.20 %</td>
</tr>
<tr>
<td></td>
<td>Impurity G</td>
<td>0.03 %</td>
<td>NMT 0.10 %</td>
</tr>
<tr>
<td></td>
<td>Individual unknown impurity</td>
<td>0.05 %</td>
<td>NMT 0.50 %</td>
</tr>
<tr>
<td></td>
<td>Total impurity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Halides expressed as chlorides</td>
<td>Less than 100 ppm</td>
<td>NMT 100 ppm</td>
</tr>
<tr>
<td>07</td>
<td>Sulphates</td>
<td>Less than 100 ppm</td>
<td>NMT 100 ppm</td>
</tr>
<tr>
<td>08</td>
<td>Heavy metals (Test C)</td>
<td>Less than 20 ppm</td>
<td>NMT 20 ppm</td>
</tr>
<tr>
<td>09</td>
<td>Loss on drying (At 60°C/Vacuo)</td>
<td>0.16 % w/w</td>
<td>NMT 0.50 % w/w</td>
</tr>
<tr>
<td>10</td>
<td>Sulphated ash</td>
<td>0.05 % w/w</td>
<td>NMT 0.10 % w/w</td>
</tr>
<tr>
<td>11</td>
<td>Assay (By HPLC)</td>
<td>98.90 %</td>
<td>NLT 98.5 % and NMT 101.0 %</td>
</tr>
<tr>
<td></td>
<td>(On dried basis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional tests:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Particle size (By Malvern mastersizer)</td>
<td>96.13 %</td>
<td>90 % particles should be less than 20 μm</td>
</tr>
</tbody>
</table>

Batch complies with respect to above specification.

S.O.No.9526954

Date: 06/03/07

Prepared by

Checked by

Approved by
### 3.6.3 Ezetimibe

#### Analytical Development Laboratory Certificate of Analysis

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Tests</th>
<th>Observations</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Description</td>
<td>White colored powder</td>
<td>White to off white powder.</td>
</tr>
<tr>
<td>02</td>
<td>Solubility</td>
<td>Complies</td>
<td>Freely soluble in Methanol, Ethanol, and Acetone.</td>
</tr>
<tr>
<td>03</td>
<td>Identification by a)IR</td>
<td>Complies</td>
<td>IR absorption spectrum of the sample in KBr dispersion should concordant with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the spectrum of Ezetimibe Reference standard.</td>
</tr>
<tr>
<td>04</td>
<td>Loss on drying</td>
<td>0.14% w/w</td>
<td>Not more than 0.5% w/w</td>
</tr>
<tr>
<td>05</td>
<td>Sulphated Ash</td>
<td>0.05% w/w</td>
<td>Not more than 0.2% w/w</td>
</tr>
<tr>
<td>06</td>
<td>Heavy metals</td>
<td>Less than 20 ppm</td>
<td>Not more than 20 ppm</td>
</tr>
<tr>
<td>07</td>
<td>Specific optical rotation (η=3%, in Methanol)</td>
<td>&lt; 27.2°</td>
<td>Between -25.0° and -34.0°</td>
</tr>
<tr>
<td>08</td>
<td>Related substances by HPLC</td>
<td>Not Detected</td>
<td>Not more than 0.30%</td>
</tr>
<tr>
<td></td>
<td>a)EZB-1 impurity</td>
<td>0.28%</td>
<td>Not more than 0.50%</td>
</tr>
<tr>
<td></td>
<td>b)Desfluro impurity</td>
<td>0.04%</td>
<td>Not more than 0.30%</td>
</tr>
<tr>
<td></td>
<td>c)Any other impurity</td>
<td>0.34%</td>
<td>Not more than 1.0%</td>
</tr>
<tr>
<td>09</td>
<td>Assay by HPLC(On dried basis)</td>
<td>99.3% w/w</td>
<td>Between 98.0% and 102.0% w/w</td>
</tr>
<tr>
<td>10</td>
<td>Particle size</td>
<td>less than 10µm</td>
<td>90% should be less than 10µm</td>
</tr>
</tbody>
</table>

*Customer requirement*

**Remarks:** The product complies to the laid down specifications.

Compiled by: K. Sujatha  
Checked by: [Signature]  
Approved by: [Signature]
3.7 REFERENCES


44. Rudnic EM, Lausier JM, Chilamkurti RN, Rhodes CT. Studies of the utility of cross linked polyvinylpolyprrolidone as a tablet disintegrant. Drug Dev Ind Pharm. 1980, 6: 291-309.


"Engineering of Pharmaceutical Particles for Advanced Drug Delivery System" 84