

2. DRUGS SELECTED FOR THE STUDY



2. Drugs selected for the study:

The lipid lowering drug of three classes were selected for the study - [I] Bile acids sequestering agents, from this ezetimibe (EZE) was selected for the study and [II] Inhibitors of HMG-CoA reductase, from this Pravastatin (PRAVA), rosuvastatin(ROSU), simvastatin(SIMVA) and lovastatin (LOVA) were selected as single and all in combination with ezetimibe. [III] Nicotinic acid (NICO) was selected in combination with SIMVA.

2.1. Single drugs:

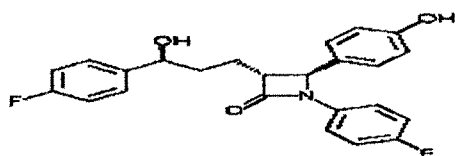
SIMVA is first line agent for the treatment of hyperlipidemia. It reduces 35% LDL – C. LOVA is structurally similar to SIMVA it have one methyl group less then simvastatin. It increases removal of LDL from the circulation. SIMVA and LOVA are prodrug. PRAVA is also similar structural to SIMVA, it increase hepatic cholesterol uptake form blood. ROSU have the same mechanism of action but it is more effective then other statin. High dose of statin have myopathy so best solution of that is EZE. EZE is potent and selective cholesterol absorption inhibitors that inhibit the transport of cholesterol across the intestinal wall.

2.1.1 Ezetimibe

EZE is an anti-hyperlipidemic medication which is used to lower cholesterol levels. It acts by decreasing cholesterol absorption in the intestine. It may be used alone when other cholesterol lowering medications are not tolerated or together with statins when cholesterol levels are unable to be controlled on statins alone.

Empirical formula : $C_{24}H_{21}F_2NO_3$

Chemical Name¹ : 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxyprppyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone



Molecular weight : 409.4 gm mol⁻¹

Melting point : 164 -166°C

Description : It is a white, crystalline powder

Solubility : It is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. It is stable at ambient temperature.

Dissociation constant (pKa) : 9.66

Dose for oral administration	: 10 mg of ezetimibe
Storage	: Store at 25°C (77 °F); excursions permitted to 15-30 °C (59 -86 °F). Protect form moisture.

Identifier

CAS number	: 163222-33-1
ATC code	: C10AX09
PubChem	: 150311
DrugBank	: APRD00619

Pharmacokinetic data

Bioavailability	: 35–65%
Protein binding	: >90%
Metabolism	: Intestinal wall, hepatic
Half life	: 19–30 hours
Excretion	: Renal 11%, faecal 78%

Clinical Pharmacology²

Mechanism of action: Ezetimibe do not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes and appears to act 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 HMG-CoA reductase inhibitors.

Pharmacokinetics: After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide. It has ability to achieve peak plasma concentration in 1-2 h. Orally it can be administered with or without food. Ezetimibe is rapidly metabolized in the small intestine and liver via glucuronide conjugation (a Phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 h for both ezetimibe and ezetimibe-glucuronide through feces and urine.

Indications and Usage: Ezetimibe, administered alone, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination Therapy with HMG-CoA reductase Inhibitors: EZE, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HOFH): The combination of Ezetimibe and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as and adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia: Ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Contraindications: Hypersensitivity, pregnancy and lactation.

Adverse effects: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, urticaria; arthralgia; myalgia; elevated creatine phosphokinase, myopathy/rhabdomyolysis, elevation in liver transaminases, hepatitis, pancreatitis, thrombocytopenia, nausea, cholelithiasis, cholecystitis.

Drug interactions: Co-administration of ezetimibe with cholestyramine decreases mean AUC of total and ezetimibe, with mean reduction of approximately 55% and 80%. The combination of ezetimibe with statins should be administered ≥ 4 h after ingestion of bile acid sequestrant and it should not be treated above the starting dose of 10 mg/day. Stable doses of cyclosporine increase the mean AUC and C_{max} values of total ezetimibe 3.4- fold and 3.9-fold, respectively, compared to a historical healthy control population (n = 17).

Precautions: Concurrent administration of ezetimibe with a specific HMG-CoA reductase inhibitor should be in accordance with the product labeling for that HMG-CoA reductase inhibitor.

Marketed formulation

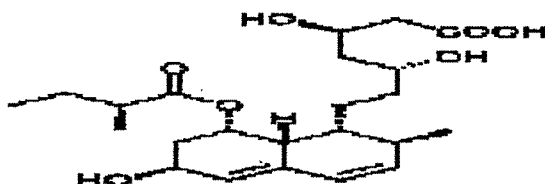
Sr. No.	Trade Name	Dose	Company
1	EZDOC	10 mg	Pinnacle (Lupin)
2	EZEE	10 mg	Genix
3	EZETIB	10 mg	Unisearch
4	ZETICA	10 mg	Delta(Torrent)

2.1.2 Pravastatin

Empirical formula

: $C_{23}H_{36}O_7$ Chemical Name¹

: 3,5-dihydroxy-7- [6-hydroxy-2-methyl-8-(2-methylbutanoyloxy)- 1,2,6,7,8,8a-hexahydronaphthalen-1-yl]- heptanoic acid



Molecular weight

: 424.528 g/mol

Melting point

: 138-142°C

Description

: White to off white crystalline powder

Solubility

: Freely soluble in water, methanol. Insoluble in chloroform ether, acetone and acetonitrile.

Dose for oral administration

: 20 –40 mg given as a single dose with evening meal

Storage

: Store at 25 C, protect from light

Identifier

CAS number

: 81093-37-0

ATC code

: C10AA03

PubChem

: 54687

DrugBank

: APRD00328

Pharmacokinetic data

Protein binding

: 50%

Metabolism

: Hydroxylation, no active metabolites.

Half life

: 2-3 hours

Excretion

: 93 % biliary, 6% renal.

Clinical Pharmacology

Mechanism of action: It inhibits HMG CoA reductase, the enzyme which catalyses the rate limiting step within the cholesterol biosynthetic pathway.

Indications and usage: Mainly use in hypercholesterolemia, mixed hyperlipidaemia, Secondary prevention of myocardial infarction and renal impairment. Usual dosage is 10 to 40 mg in a single dose

Contraindication: Cyclosporine, nefazodone, nicotinic acid increase risk of myopathy or rhabdomyolysis use lowest effective dose. Gemfibrozil increases risk of myopathy or rhabdomyolysis. Bile acid binding resins reduce bioavailability of Pravastatin; given Pravastatin at least 1 hr resin.

Adverse effects: Myopathy, mild transient gastrointestinal symptoms, headache, insomnia, dizziness, myalgia, hypersensitivity, anaphylaxis, angioedema, toxic epidermal necrolysis, delayed wound healing, rhabdomyolysis, renal failure, hepatitis, alopecia, paraesthesia, impotence.

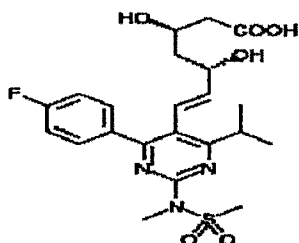
Marketed formulation

Sr. No.	Tread Name	Dose	Company
1	PRAVATOR	10 mg and 20 mg	Solus(Ran)

2.1.3 Rosuvastatin

Empirical formula : $C_{22}H_{28}FN_3O_6S$

Chemical Name : 7-[4-(4-fluorophenyl) -6-(1-methylethyl)- 2-(methyl-methylsulfonyl-amino)- pyrimidin-5-yl]- 3,5-dihydroxy-hept-6-enoic acid



Molecular weight : 481.539

Dose for oral administration : 2.5 – 20 mg

Storage : Store at 25 C and protect from light and moisture

Identifier

CAS number : 287714-41-4

ATC code : C10AA07

PubChem : 6439133

Drug Bank : APRD00546

Pharmacokinetic data

Bioavailability : 20 %

Metabolism : Liver

Half life : 19 hours

Excretion : Urine / Faeces

Clinical Pharmacology

Mechanism of action: Rosuvastatin is a selective and competitive inhibitor of HMG CoA reductase. The rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. Rosuvastatin increases the number of hepatic LDL receptors on the cell surface, enhancing uptake and catabolism of LD and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Indications and usage: Primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidemia. Rosuvastatin may be given at any time of day, with or without food. Safety and efficacy have not been established in the children elderly and dose adjustment is not necessary.

Contraindications: Cyclosporine, warfarin, gemfibrozil, erythromycin, antacids, oral contraceptive/hormone replacement therapy.

Adverse effects: Headache, dizziness, constipation, proteinuria, nausea, abdominal pain, myalgia and asthenia.

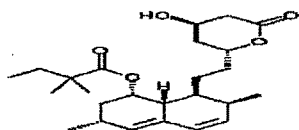
Marketed formulation

Sr. No.	Tread Name	Dose	Company
1	NOVASTAT	5, 10, 20 mg	Pinnacle (Lupin)
2	ROSTAR	5, 10 mg	Genix
3	ROSUVAS	5, 10, 20 mg	Unisearch
4	ROSUVASTAT	1000 mg	Delta(Torrent)

2.1.4 Simvastatin

Empirical formula : $C_{25}H_{38}O_5$

Chemical Name : [(1*S*,3*R*,7*R*,8*S*,8*aR*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxo-oxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8*a*-hexahydronaphthalen-1-yl]2,2-dimethylbutanoate



Molecular weight : 418.566 g/mol

Melting point : 135-138°C

Description : White crystalline powder

Solubility : Insoluble in water, n hexane and hydrochloric acid.
Soluble in chloroform, dimethylsulfoxide, methanol, ethanol, PEG, NaOH and propylene glycol.

Dose for oral administration : 5 – 40 mg per day

Storage : Store at 25C and protect from light

Identifier

CAS number : 79902-63-9

ATC code : C10AA01

PubChem : 54454

Drug Bank : APRD00104

Pharmacokinetic data

Bioavailability : 5%

Protein binding : 95%

Metabolism : Hepatic (CYP3A4)

Half life : 3 hours

Excretion : Renal 13%, faecal 60%.

Clinical Pharmacology

Mechanism of action: It is a prodrug which gets biaciveated in the liver to form the active beta-hydroxyacid derivative. This inhibits the conversion of HMG-Co A to mevalonic acid by blocking the enzyme HMG-CoA reducatates, an early and rate limiting step in the biosynthesis of cholesterol. Simvastatin has been demonstrated to reduce total cholesterol, LDL-cholesterol, and triglycerides by 25%, 35% and 10% respectively; increase in HDL is up to 12%.

Indications and Usage: Oral hypercholesterolemia with I.H.D; hypercholesterolemia in type IIa and type IIb; combined hypertriglycerideia and hypercholesterolemia. Adult: initially 5-10 mg OD in the evening. Dosage individualized and dose adjustments made at intervals of 4 weeks or more.

Contraindications: May cause slight elevation of serum digoxin. Chlestyramine and colestipol decrease bioavailability of simvastatin. Immunosuppressants , itraconazole, gemfibrozil, niacin or erythromycin with concurrent simvastatin may increase the risk of rhabdomyolysis and acute renal failure.

Adverse effects: Headache, nausea, flatulence, heart buren, absominal pain, diarrhea/constipation, dysgeusia, myopathy, hypersensitivity.

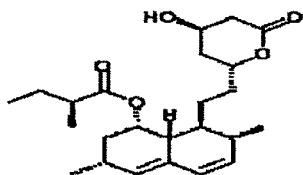
Marketed formulation

Sr. No.	Tread Name	Dose	Company
1	STATIN	5, 10 mg	Unisearch
2	SIM	5, 10, 20 mg	Mano
3	SIMCARD	5, 10, 20 mg	Cipla
4	SIMCHOL	5, 10, 20 mg	Otsira
5	SIMLO	5, 10 mg	Ipca
6	SIMVAS	5, 10, 20 mg	Carsyon (Micro)

2.1.5 Lovastatin

Empirical formula : $C_{24}H_{36}O_5$

Chemical Name : [8-[2-(4-hydroxy-6-oxo-oxan-2-yl)ethyl] -3,7-dimethyl-1,2,3,7,8,8a- hexahydronaphthalen- 1-yl] 2-methylbutanoate



Molecular weight : 404.54 g/mol

Melting point : 175.5°C

Description : White crystalline powder

Solubility : Insoluble in water, n hexane and hydrochloric acid. Soluble in chloroform, dimethylsulfoxide, methanol, ethanol, PEG, NaOH and propylene glycol.

Dose for oral administration : 10 – 80 mg per day once or twice

Storage : Store at 25°C and protect from light

Identifier

CAS number : 75330-75-5

ATC code : C10AA02

PubChem : 53232

DrugBank : APRD00370

Pharmacokinetic data

Bioavailability : <5%

Protein binding	: >95%
Metabolism	: Hepatic (CYP3A substrate)
Half life	: 1.1-1.7 hours
Excretion	: Negligible

Clinical Pharmacology

Mechanism of action: It is a prodrug which gets biaciveated in the liver to form the active beta-hydroxyacid derivative. This inhibits the conversion of HMG-Co A to mevalonic acid by blocking the enzyme HMG-CoA reducatas, an early and rate limiting step in the biosynthesis of cholesterol. Action is mainly in the liver and results in increase of hepatic LDL receptors. There is increased removal of LDL from the circulation.

Indications and Usage: Oral hypercholesterolemia with I.H.D; hypercholesterolemia in type IIa and type IIb; combined hypertriglycerideia and hypercholesterolemia. Dosage individualized and dose adjustments made at intervals of 4 weeks or more.

Contraindications: Coumarin anticoagulants, bleeding or increased prothrombin time, gemfibrozil, nicotinic acid, immunosuppressants, erythromycin.

Adverse effects: Flatulence, nausea, heartburn, constipation or diarrhea, abdominal pain and cramps, myalgia, weakness, blurred vision, lens opacities, headache, dizziness, rash, pruritus, impotence.

Marketed formulation

Sr. No.	Tread Name	Dose	Company
1	AZTATIN	10, 20 mg	Sun
2	ELSTATIN	10, 20 mg	Glenmark
3	LOVALIP	10, 20 mg	Cadila pharma
4	LOVAMEG	20 mg	Alembic
5	LOVASTAT	20 mg	Torrent
6	LOVATIN	10, 20 mg	Intas
7	STATIN	10, 20 mg	Unichem

2.1.5. Nicotinic acid

Empirical formula	: $C_6H_5NO_2$
Chemical Name	: Nicotinic acid (pyridine-3-carboxylic acid)



Molecular weight	: 123.11 g/mol
Melting point	: 236.6 °C
Description	: White crystalline powder
Solubility	: Freely soluble in methanol and water, soluble in ACN.
Dose for oral administration	: 10 – 80 mg per day once or twice
Storage	: Store at 25°C and protect from light
Identifier	
CAS number	: 59-67-6
PubChem	: 938

Clinical Pharmacology

Mechanism of action: Nicotinamide raises HDL-cholesterol and lower LDL-cholesterol.

Indications and Usage: Hyperlipidaemia.

Contraindications: Ganglionic blocking agents, HMG-CoA reductase inhibitor.

Adverse effects: Vomiting, diarrhoea, peptic ulceration, jaundice, decreased glucose tolerance, hyperuricaemia, hyperpigmentation, dry skin and headache.

Marketed formulation

Sr. No.	Tread Name	Dose	Company
1	SIMVOTIN TAB	5(SIMVA)+ 125(NICO) mg	Ranbaxy

2.2 Combinations of HMG Reds with ezetimibe drugs^{3,4}

The most recent guidelines to recommend the reduction of low-density lipoprotein cholesterol (LDL-C) as the primary target of treatment, but the optimum level of LDL-C has been lowered and statins are considered first line drugs for attaining this goal. However, statin monotherapy may not always be optimal for patients with significant combined or mixed dyslipidemias (e.g., elevated low-density lipoprotein cholesterol plus hypertriglyceridemia) or with concomitant conditions that increase the patient's level of risk (e.g., type 2 diabetes, hypertension or metabolic syndrome).

Combination therapeutic modalities are often required for optimal lipid management. Combining agents from different classes can be effective, well tolerated, and safe in most patients. Combination drug therapy, which utilizes complementary mechanisms of action to reduce one or more lipoprotein, may be preferable. Ezetimibe is a newer cholesterol absorption inhibitor, which is safe, effective and well-tolerated drug. It is given in once a day dose because of longer half-life of > 24 hours. The addition of Ezetimibe to statin therapy provides an effective means for further 23% reduction in LDL levels.⁵ The combination is more potent and safe than the statin alone as with each two-fold increase in dose of statin, there is only additional 7% reduction in LDL, associated with two fold increase risk of impaired liver enzymes.⁶ the combination regimen is well tolerated across the wide dose range of different statins. Co-administration of Ezetimibe with statin offers a new approach to LDL reduction while avoiding high doses of statins, thus providing practitioners with a sage, convenient alternative to stepwise statin titration. Presently, with the limited available data on the drug safety and efficacy, the combination therapy might be indicated/useful in following conditions: (1) High dose of statin is required to achieve the LDL goals, which is associated with significant increase in liver and muscle toxicity-clinical or laboratory based. (2) Statins alone is not sufficient to achieve the LDL goals. Addition of fibrates/niacin with statins may have the adjunctive role in treatment with high triglycerides/low HDL, but the combination is associated with increased incidence of abnormal muscle and liver enzymes and is not as effective as Ezetimibe statin combination in LDL reduction. Rosuvastatin, a potent statin presently available in the market, when combined in low doses i.e. 10-20 mg/day; with Ezetimibe can be a most potent and sage combination for reduction of LDL-C. (3) Patient unable to tolerate statins. As monotherapy, Ezetimibe is a weak hypolipidemic drug with only 18.5% reduction in LDL. In such situation, bile acid sequesterants may be a good alternative, which reduces LDL to the tune of 30%. But again, Ezetimibe is well tolerated compared to bile acid sequesterants. Like other lipid lowering drugs, the long term safety, efficacy and impact on cardiovascular morbidity and mortality with Ezetimibe is lacking and there is a need to evaluate this aspect in future long term.

Table 1.1: Efficacy of various statins in LDL-Cholesterol Lowering⁶

Dose of Statin in mg/day						% Reduction in LDL-C
ROSU	ATORVA	SIMVA	LOVA	PRAVA	FLUVA	
-	-	10	20	20	40	27
-	10	20	40	40	80	34
5	20	40	80	-	160	41
10	40	80	-	-	-	48
-	80	-	-	-	-	55

-10 mg Simvastatin + 10 mg Ezetimibe per day results in 44% reduction in LDL.⁷

-10 mg Atorvastatin + 10 mg Ezetimibe per day results in 50% reduction in LDL.^{7,8}

-There is additional 15-20% reduction in LDL, 9% reduction in triglycerides and 3% increase in HDL-C, when used in combination V/S statins alone.¹⁰

Ezetimibe and Simvastatin¹¹

Ezetimibe and Simvastatin in combined as a fixed dose therapy has been approved by USFDA, which offers simultaneous inhibition of two key pathways in cholesterol metabolism: (i) Hepatic cholesterol biosynthesis and (ii) the absorption of cholesterol at the level of proximal jejunum. This dual mechanism of inhibition substantially increases the capacity to decrease serum levels of atherogenic LDL and increases high-density lipoprotein (HDL), compared with that observed when either drug is used alone. This combination increases the chances of therapeutic success in patients with dyslipidemia.

Simvastatin and Nicotinic acid^{12,13}

Simvastatin with Nicotinic acid is reduce VLDL and increase in HDL concentration.

2.3 REFERENCES

1. Budavari S, Eds In. The Merck Index, 13th Edn., Merck find. Co. Inc., Whitehouse Station, N. J., 2001, 693.
2. Lily A J, Cheng J W M. Pharmacology and Therapeutics of ezetimibe, a cholesterol - absorption inhibitor. Clinical Therapeutics. 2003; 25: 2352-2387.
3. Guyton I R. Combination Drug Therapy for Combined Dyslipidemia. Curro Cardiol. Reports. 1999; 1: 244-250.
4. Worz C R, Bottorff M. Treating Dyslipidemic Patients with Lipid Modifying and Combination Therapies. Pharmacotherapy. 2003; 23: 625-637.

- 5 . Pearson T, Denke M, McBride P, Battist W, Brady W, Palmisano. Ezetimibe added to statin therapy reduce LDL-C and improves goal attainment in patients with hypercholesterolemia. Program and abstracts from the American College of Cardiology 53rd annual Scientific Session; March 7-10, 2004; New Orleans, Louisiana. Late Breaking clinical Trails III.
- 6 . Roberts W C. The rule of 5 and 7 in lipid lowering by statin drugs. *Am J Cardiol.* 1997; 80: 106- 107.
- 7 . Davidson M H, McGarry T, Bettis R. Ezetimibe co-administered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol.* 2002; 40: 2125-2134.
- 8 . Ballantyne C M, Houri J, Notarbortolo A. Ezetimibe study group. Effect of ezetimibe co-administered with atorvastatin in 625 patients with primary hypercholesterolemia; a prospective, randomize, double blind trial. *Circulation.* 2003; 107: 2409- 2415.
- 9 . Stein E, Stender S, Mata P. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *American Heart Journal.* 2004; 148: 447- 455.
- 10 . Manuro V F, Tuckerman C E. Ezetimibe for management of hypercholesterolaemia. *Ann Pharmacother.* 2003; 37: 839- 848.
- 11 . Davidson M H, McGarry T. Bettis R. Ezetimibe Coadministered with Simvastatin in Patients with Primary Hypercholesterolemia. *J. Am. Coli. a. Cardiol.* 2002; 40: 2125-2134.
- 12 . Anja V., Ursula K., Ulrike H., Elisabeth S. T. Safety and Tolerability of Prolonged-Release Nicotinic Acid Combined With a Statin in NAUTILUS.; on behalf of the NAUTILUS Study Group. *Br J Cardiol.* 2006; 13: 4: 273- 277.
- 13 . Kolovou G. D, Salpea K. D, Mihos C, Malakos I, Kafaltis N, Bilianou H. G, Adamopoulou E. N, Mykoniatis M, Cokkinos D. V. Comparison of simvastatin and nicotinic acid administration in alcohol-treated Wistar rats. *Hellenic J Cardiol.* 2008; 49: 2: 79-85.