International Archive of Applied Sciences and Technology
Int. Arch. App. Sci. Technol; Vol 4 [4]Decemebr 2013: 48-54
© 2013 Society of Education, India
[ISO9001: 2008 Certified Organization]
www.soeagra.com/iaast.html

IAAST
ONLINE ISSN 2277- 1565
PRINT ISSN 0976 - 4828

CODEN: IAASCA **REVIEW ARTICLE**

LIPTRUZET A New Drug Product For Anti-Hyperlipidemia-A Review

Sumit Kumar[1]*, Swatantra Bahadur Singh[2], Shivshankar Pandey[2]
[1] Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly, Uttar Pradesh, India
[2] Department of Pharmacy, Institute of Technology & Management, GIDA, Gorakhpur, Uttar Pradesh, India
E-mail: sumit09py52@gmail.com

ABSTRACT
Hyperlipidemia, hyperlipoproteinemia and hypercholesterolemia terminology is used to indicate the high levels of cholesterol in the blood. The calcium salt of Atorvastatin is currently used for the treatment of hypercholesterolemia. People with high cholesterol have about twice the risk of heart disease as people with lower levels. Liptruzet (atorvastatin and ezetimibe) is a statin (HMG-CoA reductase inhibitor) and cholesterol absorption inhibitor combination indicated for the treatment of hyperlipidemia. Ezetimibe is the first compound approved for lowering total and LDL-C levels that inhibits cholesterol absorption by enterocytes in the small intestine. Liptruzet treats two sources of cholesterol, with atorvastatin it reduces the production of cholesterol in the liver and with ezetimibe it inhibits the absorption of cholesterol in the digestive tract. Tablets (ezetimibe mg/atorvastatin mg): 10/10, 10/20, 10/40, 10/80. The Liptruzet is contraindicated in active liver disease or unexplained persistent elevations of hepatic transaminase levels and women who are pregnant or may become pregnant. Lipttruzet shows interaction with many drugs which causes risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole).
Key words: Hypercholesterolemia, HMG-CoA reductase inhibitor, interaction.

Received 09/08/2013 **Revised 12/09/2013** **Accepted 23/10/2013**

INTRODUCTION

Hyperlipidemia

Cardiovascular disease (CVD) is the term given to a group of the diseases of the heart and blood vessels. Cardiovascular disease includes coronary heart disease, stroke, heart failure, rheumatic fever and rheumatic heart disease, peripheral vascular disease, hypertension, hypertensive heart disease, endovascular and chronic kidney disease [1]. About 85% of CHD deaths occur in individuals over 65 years of age [2]. The incidence of Coronary heart disease (CHD) is correlated with elevated levels of low-density lipoproteins (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoproteins (HDL) cholesterol [3]. Hypolipidaemic drugs which lower the levels of lipids and lipoproteins in blood. The hypolipidaemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidemic individuals. Dietary lipids are absorbed in the intestine with the help of bile acids. The liver secretes very low density lipoprotein (VLDL) containing mainly TG and some CHE into blood [4]. Cholesterol is an essential component of cell membranes and a metabolic intermediate in the synthesis of steroid hormones and bile salt's. Some cholesterol is detained from the diet (about 25%) and the rest is manufactured by the liver. However, elevated levels in serum may be a result of high dietary intake, a condition known as exogenous hyperlipidemia or secondary hyperlipidemia. Endogenous hyperlipidemia also called primary or familial hyperlipidemia is a disorder of cholesterol metabolism that may be caused by genetic factors. This is much less common than exogenous hyperlipidemia. Diseases such as diabetes mellitus, gout, hypothyroidism and obstructive jaundice, cirrhosis of the liver and renal failure can cause secondary hyperlipidemia. Several clinical studies have shown that complex carbohydrates, such as oat bran, guar gum, and carob gum also lower serum cholesterol levels [5].

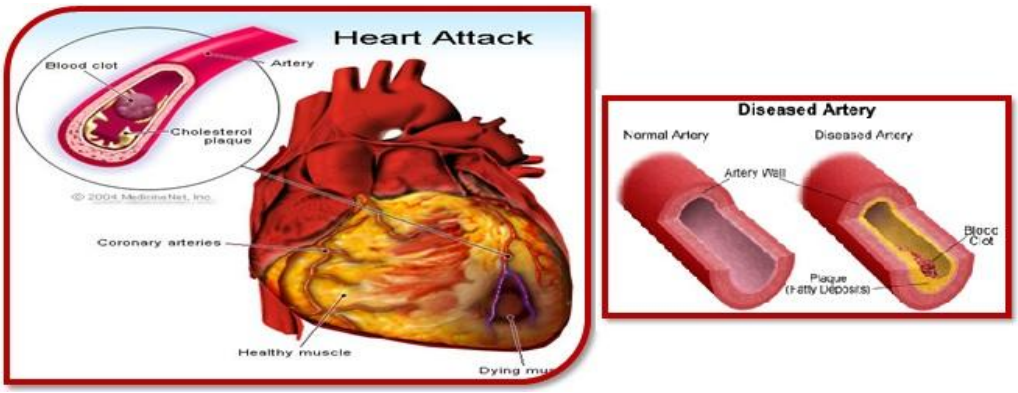


Figure 1: Schematic representation of diseased artery of human heart

The term lipids include cholesterol and triglycerides. There are many different types of lipid (also called lipoproteins). The standard lipid blood tests include a measurement of total cholesterol, LDL (low density lipoproteins), HDL (high density lipoproteins) and triglycerides.

Total cholesterol: A high total cholesterol level can increase the risk of coronary disease. However, decisions about when to treat high cholesterol are usually based upon the level of LDL or HDL cholesterol, rather than the level of total cholesterol **[6].**

Cholesterol level	Risk of CHD
> 200 mg/dL (5.17 mmol/L)	Normal
200 - 239 mg/dl (5.17- 6.18 mmol/L)	Borderline high
240 mg/dl (6.21 mmol/L)	High

Triglycerides: High triglyceride levels are also associated with an increased risk of coronary disease. Triglyceride levels are divided as follows **[7]**

Triglyceride level	Risk of CHD
> 150 mg/dL (1.69 mmol/L)	Normal
150-199 mg/dL (1.69-2.25 mmol/L)	Borderline high
200- 499 mg/dL (2.25-5.63 mmol/L)	High
< 500 mg/dL (5.65 mmol/L)	Very high

General symptoms of hyperlipidemia [3, 8]

- Formation of atheromatous plaques in the arteries
- Progressive stenosis (narrowing) or complete occlusion (blockage) of the involved arteries
- Myocardial infarction or heart attack
- Stroke

Causes of hyperlipidemia: There are two factors which are main causes of hyperlipidemia

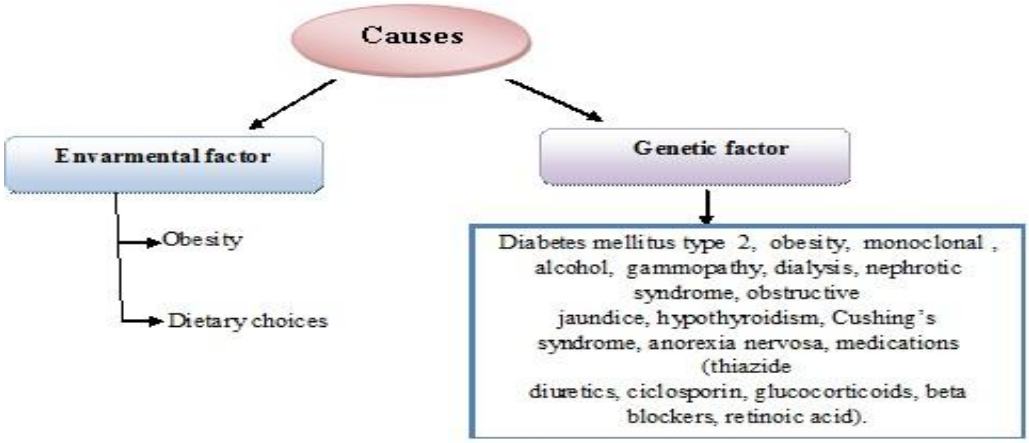


Figure 2: Different causes of hyperlipidemia

Types of hyperlipidemia [9]

3 categories of hyperlipidemia are differentiated on the basis of cholesterol and triglyceride concentration in the plasma.

- **Hypercholesterolemia > 200mg/dL (5.2 mmol/L)**
- **Hypertriglyceridemia > 150 mg/dL (1.7mmol/L)**
- **Mixed Hyperlipidemia**

Classification of antihyperlipidiemic drugs

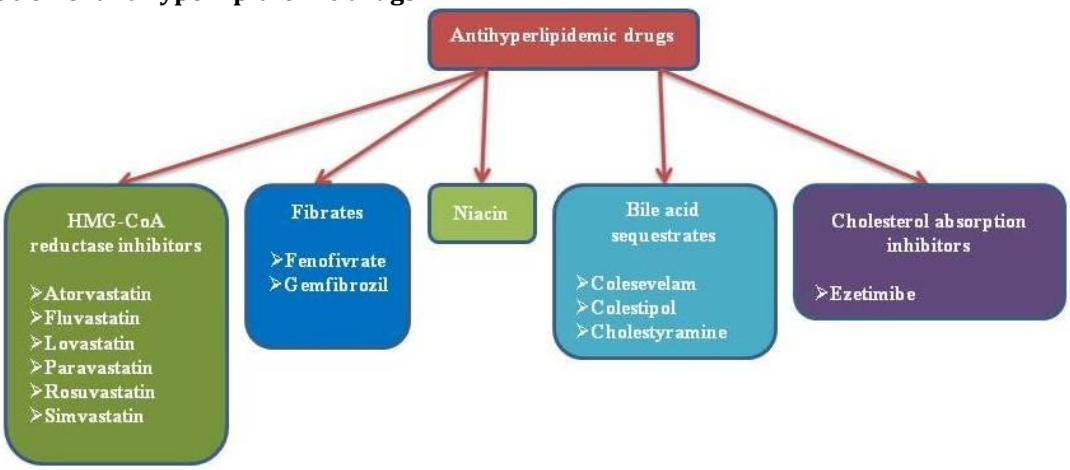


Table: 1 Different class of antihyperlipidemic drugs with their Brand name, Metabolite and side effects [10]

Medication	Brand name	Dose of 30-40% LDL reduction	Metabolism	Potentially severe side effects
(Statins) Atorvastatin	(Lipitor®)	10 mg/day	CYP 3A4 Lipophilic active metabolism	Liver failure: rare fatal rhabdomyolysis
Fluvastation	(Lescol®)	40-80 mg/day	CYP2C9 Lipophilic inactive metabolites	
Lovastatin	(Memacor®)	40 mg/day	CYP3A4 Lipophilic active metabolites	
Extended release nicotinic acid	(Niaspan®)	1-2 g/day	Balanced metabolism between the two pathways extensile liver metabolism inhibit cholesterol absorption glucuroridation	Hepatotaxicity activation of peptic ulcer disease
(Fibrates) Genfibrozil Clofibrate	(Lipid®) (Atromid®)	600 mg bid 1000 mg bid	Glucuroridation	Pancreatitis (Rate) Hepatotaxicity (rare) Rhabdomyolysis (rare)
(Cholesterol absorption inhibitors) Ezetimibe	(Zetial®)	10 mg	Inhibit cholesterol absorption Glucuroridation	Avoid in moderate severe hepatic impairment

MODERN TREATMENT OF HYPERLIPIDEMIA

Liptruzet

Liptruzet approval history [11]

FDA approved: First approved May 3rd, 2013

Brand name: Liptruzet

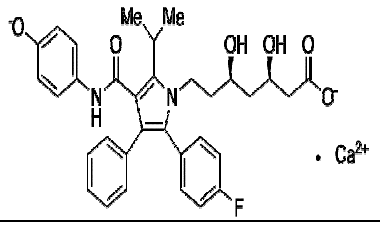
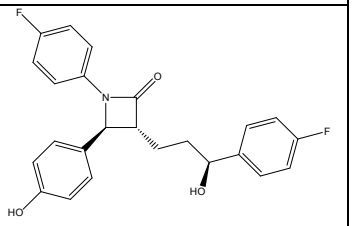
Generic name: Atorvastatin and Ezetimibe

Company: Merck

Treatment for:

- High Cholesterol
- Familial Heterozygous

Table: Chemical nature and properties of Atorvastatin and Ezetimibe [12, 13, 14]

Drug	Atorvastatin calcium	Ezetimibe
Molecular Formula	$(C_{33}H_{34}FN_2O_5)_2Ca{\cdot}3H_2O$	$C_{24}H_{21}F_2NO_3$
Molecular weight	1209.42 g.mol^{-1}	409.4252 g.mol^{-1}
Chemical structure		
Solubility	Slightly soluble in water	Insoluble in water
Melting point	>220°C	163°C
Dose size	Oral (10mg, 20mg, 40mg, 80mg)	Oral (10 mg)

PHARMACOLOGY

Atorvastatin inhibits an enzyme called HMG-CoA reductase that mediates an important step in the synthesis of cholesterol. Working through a different mechanism, ezetimibe reduces cholesterol absorption in the intestinal brush border by inhibiting a cholesterol and phyto-sterol transporter **[15].**

Mechanism of action (MOA)

Atorvastatin: HMG-CoA reductase inhibitor; lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; also reduces LDL production and the number of LDL particles.

Ezetimibe: Cholesterol absorption inhibitor; localizes at the brush border of the small intestine. Targets the sterol transporter, Neimann-Pick C1-like 1, which is involved in intestinal uptake of cholesterol and phytosterols **[16].**

Over dosage [17]

No specific treatment of over dosage with LIPTRUZET can be recommended. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Pharmacokinetic parameters [18]

Drug	Atorvastatin	Ezetimibe
Absorption	oral administration with maximum plasma concentrations achieved in 1 to 2 hours	After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide)
Half-life	14 hours	19-30 hours
Plasma protein binding	≥98%	>90%
Metabolism	CYP3A4 (extensive); ortho and parahydroxylated derivatives (active metabolites)	Intestinal wall, hepatic
Elimination	Bile (major), urine (<2%)	Faeces (78%, 69% unchanged drug), urine (11%, 9% metabolite)

Drug Interactions [18]

There are more drugs listed which show interaction with **Liptruzet:**

- Colchicine
- Cyclosporine
- Digoxin, digitalis
- Imatinib
- Isoniazid
- Nefazodone
- Niacin, vitamin B_3
- An antibiotic-clarithromycin, erythromycin, rifampin, telithromycin
- antifungal medication-itraconazole, ketoconazole, posaconazole, voriconazole
- Birth control pills
- A blood thinner (warfarin, Coumadin)
- Heart medication--nicardipine, quinidine
- Hepatitis C medications--boceprevir, telaprevir
- HIV/AIDS medication-atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, tipranavir
- Other cholesterol medications, especially fenofibrate, fenofibric acid, gemfibrozil, or any other "statin" medicine
- Seizure medication-carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone
- Tuberculosis medication-rifabutin, rifampin, rifapentine

Contraindications [19]

- Hypersensitivity
- Active liver disease or unexplained elevated transaminases
- Women who are pregnant or may become pregnant
- Breast feeding women

Warnings and precautions [20]

- Patients should be advised to report promptly any unexplained and/or persistent muscle pain, tenderness, or weakness. LIPTRUZET should be discontinued immediately if myopathy is diagnosed or suspected.
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain CYP3A4 inhibitors, fibric acid derivatives, and cyclosporine. Predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported.
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminase can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.



Figure 7: LIPTRUZET 10mg/20mg tablet the brand of Merck & Co., Inc

Uses [21]

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet

restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

Storage conditions [16]

20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Store in foil pouch until use. Protect from moisture and light and store in a dry place after the foil pouch is opened. Once a tab is removed, slide blister card back in the case. Discard any unused tab 30 days after the pouch is opened.

USE IN SPECIFIC POPULATIONS

Pregnancy

- Pregnancy Category **X**
- LIPTRUZET is contraindicated in women who are or may become pregnant.
- There are no adequate and well-controlled studies of LIPTRUZET use during pregnancy. Statins may cause fetal harm when administered to a pregnant woman. Because LIPTRUZET contains atorvastatin, LIPTRUZET should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards

Nursing Mothers

Because of the potential for adverse reactions in nursing infants, women taking LIPTRUZET should not breast-feed.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

The effectiveness and safety of LIPTRUZET were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, LIPTRUZET should be prescribed with caution in the elderly.

In geriatric patients, no dosage adjustment of LIPTRUZET is necessary.

Hepatic Impairment

LIPTRUZET is contraindicated in patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels.

Gender

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Lipitor between men and women.

Haemodialysis

While studies have not been conducted in patients with end-stage renal disease, haemodialysis is not expected to significantly enhance clearance of Atorvastatin since the drug is extensively bound to plasma proteins **[22].**

Renal Impairment

A history of renal impairment may be a risk factor for statin-associated myopathy. These patients merit closer monitoring of skeletal muscle effects.

In patients with renal impairment, no dosage adjustment of LIPTRUZET is necessary **[23].**

Key factors [24, 25]

- Rates of high total cholesterol in the United States in 2010 are just over 13% down from 17% in 2000.
- For healthy adults, the UK National Health Service recommends total cholesterol of 5 mmol/L or less, and low-density lipoprotein cholesterol (LDL) of 3 mmol/L or less. For people at high risk of cardiovascular disease, the recommendation for total cholesterol is 4 mmol/L or less, and 2 mmol/L or less for LDL.
- Average total cholesterol in the United Kingdom is 5.9 mmol/L while in rural China and Japan average total cholesterol is 4 mmol/L. Rates of coronary artery disease are higher in Great Britain, but low in rural China and Japan.
- 50% of the population have an increased plasma lipid level, resulting in increased risk of coronary heart disease
- 71 million American adults (33.5%) have high low-density lipoprotein (LDL), or "bad" cholesterol.
- Only 1 out of every 3 adults with high LDL cholesterol has the condition under control.
- <50% of individuals over 40 years old in the western world have hypercholesterolemia.

ACKNOWLEDGEMENT

I would like to express my heartiest gratitude to Dr. Shashi Bhooshan Tiwari, Associate professor, Department of Pharmacy M.J.P. Rohilkhand University, Bareilly, the guide of the project for guiding and correcting various documents of mine with attention and care.

REFERENCES

1. Review of cardiovascular disease programs, Final report, Dept. of health and ageing, 30 mach. (2009), pp-3.
2. Goodman & Gilman's, (2001).The pharmacological basis of therapeutics, 11th edition, McGraw-Hill medical publishing division, pp-933.
3. Richard D. Howland, Mary J. Mycek, (1998). Lippincott's Illustrated reviews: Pharmacology 3rd edition, New Delhi, pp-245.
4. Tripathi K.D., (1999). Essentials of medical pharmacology, 6th edition, Jaypee brothers 'medical publishers (P) Ltd. New Delhi, pp- 612-613.
5. David Hoffmann, (2003). Medical pierbalism: The science and practice of Herbal medicine, Healing Art press pp-171.
6. Available from (2013). http://www. uptodate. Com / contents / high- cholesterol -and- lipids-hyperlipidemia-beyond-the-basics (access to 20/09/2013).
7. R.S. Satoskar, S. D. Bhandarkar, Pharmacology and Pharmacotherapeutics, 12th edition, popular prakashan, pp-576.
8. Available from https://www.clinicalkey.com/topics/cardiology/hyperlipidemia.html (access to 23/09/2013).
9. Gabriele Staffers, (2012). Susanne Credner, general pathology and internal medicine for physical Therapists, Georg Thieme Verlag.
10. Brian V. Reamy, (2008). Hyperlipidemia management for primary care, Springer, pp-146 148.
11. Available from http://www.drugs.com/history/liptruzet.html.
12. Available from http://www.rxlist.com/liptruzet-drug.h.
13. Farzana Akter Popy, Irin Dewan, Most, Nazma Parvin, S. M. Ashraful Islam. (2013). Evaluation of In vitro equivalence for tablets containing the poorly water-soluble compounds Atorvastatin, Dissolution Technologies. pp-1.
14. http://www.drugfuture.com/chemdata/atorvastatin.html.
15. http://www.pharmacytimes.com/publications/issue/2013/August2013/Mercks-Liptruzet.
16. http://www.pdr.net/drug-summary/liptruzet?druglabelid=3110
17. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c387354c-607b-474d-b2e5-5c789ce09b#nlm3408..
18. http://www.drugs.com/liptruzet.html (access to 01/10/2013)
19. http://reference.medscape.com/drug/liptruzet-atorvastatin-ezetimibe-999849 (access to 03/10/2013)
20. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c387354c-607b-474d-b2e5-d 35c 789 ce0 9b # section- 7 (access to 03/10/2013)
21. http://www.drugs.com/pro/liptruzet-tablets.html (access to 05/10/2013)
22. http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/20702s25lbl.pdf (access to 05/10/2013)
23. http://www.drugs.com/pro/liptruzet-tablets.html#S12.3 (access to 05/10/2013)
24. http://en.wikipedia.org/wiki/Hypercholesterolemia (access to 06/10/2013)
25. http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_cholesterol.htm (access to 09/10/2013)

Ciation of this article

Sumit Kumar, Swatantra Bahadur Singh, Shivshankar Pandey. LIPTRUZET A New Drug Product For Anti-Hyperlipidemia-A Review. Int. Arch. App. Sci. Technol; Vol 4 [4]Decemebr 2013: 48-54