DESCRIPTION

Fixed dose combination of Atorvastatin and Ezetimibe contains Atorvastatin which is chemically [R-(R*, R*)]-2-(4-fluorophenyl)-ß,d-dihydroxy-5- (1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, Calcium salt and Ezetimibe which is (3R,4S)-1-(4-Fluorophenyl)-(3R)-[(3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone.

LowerTM is a yellow coloured, oblong, biconvex, film coated tablet.

COMPOSITION

LowerTM
Each film-coated tablet contains:
Atorvastatin Calcium equivalent to Atorvastatin........... 10 mg
Ezetimibe.......................................... 10 mg
Colours: Ferric Oxide and Titanium Dioxide

CLINICAL PHARMACOLOGY

Mechanism of action

Atorvastatin
Atorvastatin belongs to the category of statins, which inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Synthesis of mevalonic acid is impeded, which is a rate-limiting step in cholesterol biosynthesis. This results in a decrease in intracellular cholesterol leading to an increase in the number of synthesis of LDL receptors and increased clearance of LDL cholesterol in plasma. HMG-CoA reductase inhibitors may also lower plasma cholesterol levels by decreasing hepatic production of VLDL and LDL cholesterol

Ezetimibe
Ezetimibe is a selective cholesterol absorption inhibitor, which potently and selectively prevents absorption of cholesterol from dietary and biliary sources by preventing transport of cholesterol through the intestinal wall. This reduces the overall delivery of cholesterol to the liver, thereby promoting the synthesis of LDL receptors and a subsequent reduction in serum LDL-C. Ezetimibe does not affect the absorption of fat-soluble vitamins
RATIONALE OF COMBINATION

Atorvastatin is a selective HMG-CoA reductase inhibitor and causes a decrease in intracellular cholesterol levels and an increased clearance of LDL cholesterol in plasma. Ezetimibe is a selective cholesterol absorption inhibitor, which potently and selectively prevents absorption of cholesterol through the intestinal wall.

Since decrease in LDL receptors and HDL cholesterol is observed in hyperlipidemia, the use of both Atorvastatin and Ezetimibe in combination produces additive effects in hyperlipidemia. Atorvastatin when used in combination with Ezetimibe causes manifold reduction in LDL cholesterol levels as compared to double the dose of the individual drug when used alone. Moreover, the use of Ezetimibe with Atorvastatin allows for an enhanced effect of the statin at a lower dose and reduction in associated side effects.

PHARMACOKINETICS

Atorvastatin

After oral administration, Atorvastatin is rapidly absorbed, with peak serum concentrations reaching within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of Atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%.

Mean volume of distribution is approximately 381 liters. Atorvastatin is ≥ 98% bound to plasma proteins.

Atorvastatin is extensively metabolized to ortho- and para hydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulatory inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of Atorvastatin in humans is approximately 14 hrs, but the half life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to contribution of active metabolites.

Ezetimibe

Ezetimibe is rapidly absorbed and conjugated after oral administration. \( T_{\text{max}} \) of Ezetimibe and Ezetimibe-glucuronide are 4-12 hrs and 1-2 hrs respectively. Concomitant food administration (high fat or non-fat meals) has no effect on the extent of absorption of Ezetimibe. Ezetimibe can be administered with or without food.

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

In humans, Ezetimibe gets rapidly metabolized to Ezetimibe-glucuronide. Ezetimibe and Ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10-20% and 80-90% of the total drug in plasma, respectively. Both Ezetimibe and Ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both Ezetimibe and Ezetimibe-glucuronide.

From the pharmacokinetic profile, it is clear that both the drugs are rapidly absorbed after oral administration with their long \( T_{\text{1/2}} \) for elimination supporting once daily therapy. The \( T_{\text{max}} \) for Atorvastatin and Ezetimibe glucuronide (pharmacologically active metabolite of Ezetimibe) are
also same (i.e. 1-2 hours) which further supports their use in fixed dose combination as a single
dose. Further Atorvastatin and Ezetimibe can be administered as a single dose at any time of the
day with or without food.

SPECIAL POPULATIONS

Elderly
Treatment of Atorvastatin and Ezetimibe individually in adults greater than 70 years is same as
those below 70 years of age.
Based on the studies of Atorvastatin alone, the C\text{max} of Atorvastatin was 42.8% higher in elderly
patients than in young participants and 17.6% higher in women than men. In addition, the mean
area under the concentration time curve and half life were 27.3% greater and 36.2% longer,
respectively, in elderly than in young adults and 11.3% lower and 19.9% shorter, respectively, in
women than in men\textsuperscript{5}
In a multiple dose study with Ezetimibe given 10mg once daily for 10 days, plasma
concentrations for total Ezetimibe were about 2-fold higher in older (>65 years) healthy subjects
compared to younger subjects.

Pediatric use
Treatment of Atorvastatin and Ezetimibe is not recommended in children below 10 years of age.

Hepatic dysfunction
The pharmacokinetics and tolerability of this combination in patients with impaired hepatic
function has not been studied. Since Atorvastatin and Ezetimibe are both extensively metabolized
by the liver, its use in patients with hepatic impairment is not recommended.

Renal dysfunction
There is no data available on the pharmacokinetics of this combination in patients with renal
impairment. Based on studies using Atorvastatin alone, renal disease does not influence the
plasma concentrations or LDL cholesterol levels of Atorvastatin.

CLINICAL STUDIES

Atorvastatin
Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients
with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks,
and maximum response is usually achieved within 4 weeks and maintained during chronic
therapy\textsuperscript{1}.

Atorvastatin is effective in a wide variety of patient populations with hypercholesterolemia, with
and without hypertriglyceridemia, in men and women, and in the elderly. In two multicenter,
placebo-controlled, dose-response studies in patients with hypercholesterolemia, Atorvastatin
given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG.\textsuperscript{8}

Ezetimibe
In pooled analysis of two, phase III studies on effectiveness and tolerability of Ezetimibe in
patients with primary hypercholesterolemia, Ezetimibe has shown a significant decrease in
plasma LDL-C levels.\textsuperscript{7}
In two, multicenter, double blind, placebo controlled, 12 week studies in 1719 patients with
primary hypercholesterolemia, Ezetimibe significantly lowered total LDL-C, apo B and TG, and
increased HDL-C compared to placebo\textsuperscript{8}
Co-administration of Atorvastatin and Ezetimibe
In a prospective, randomized, double blind trial conducted for effect of Ezetimibe co-administered with Atorvastatin in 628 patients with primary hypercholesterolemia; the coadministration of Atorvastain and Ezetimibe provided significant incremental reduction in LDL-C and triglycerides and increases in HDL-C.

Table: Response to Atorvastatin and Ezetimibe combination in patients of Primary Hypercholesterolemia: Percent changes from baseline

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Atorvastatin 10 mg + Ezetimibe 10 mg</th>
<th>Atorvastatin 20mg + Ezetimibe 10 mg</th>
<th>Atorvastatin 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>- 50%</td>
<td>- 54%</td>
<td>-51%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>- 31%</td>
<td>- 30%</td>
<td>-31 %</td>
</tr>
<tr>
<td>HDL-C</td>
<td>9%</td>
<td>9%</td>
<td>3 %</td>
</tr>
</tbody>
</table>

The mean reduction in the levels of LDL-C, triglycerides from baseline with Atorvastatin 10 mg and Ezetimibe 10 mg co-administration was 50% and 31% respectively while mean increase in HDL was 9%. The mean reduction in the levels of LDL-C, triglycerides from baseline with Atorvastatin 20 mg and Ezetimibe 10 mg was 54% and 30% respectively while mean increase in HDL was 9%. LDL-C and triglyceride reductions with Ezetimibe plus 10 mg Atorvastatin (50% and 31%) and 80 mg Atorvastatin alone (51% and 31%) were similar while mean increase in HDL with Atorvastatin 10 mg plus Ezetimibe 10 mg was more than Atorvastatin 80 mg alone (9% and 3%).

Another study demonstrated that adding Ezetimibe 10mg to Atorvastatin 10mg resulted in an LDL cholesterol lowering that is comparble to a 3 step titration of the statin dose to 80mg.

In a study on efficacy and safety of Ezetimibe co-administered with Atorvastatin in patients with homozygous familial hypercholesterolemia, it was concluded that the co-administration in patients with homozygous familial hypercholesterolemia (HoFM) produces clinically important LDL-C reductions compared with best current therapy.

INDICATIONS AND USAGE
The FDC is indicated for the treatment of patients with primary hypercholesterolemia.

CONTRAINDICATIONS
Patients with known hypersensitivity to Atorvastatin and/or Ezetimibe.
Evidence of acute liver disease or unexplained persistent elevations of serum transaminases.

WARNINGS AND PRECAUTIONS
Atorvastatin
**Hepatic dysfunction**
Atorvastatin should be used with caution in patients who consume substantial quantity of alcohol and/or have a history of liver disease.

**Skeletal muscle**
Caution should be taken in rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria. Uncomplicated myalgia has also been reported in Atorvastatin-treated patients.

**Endocrine Function**
HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as Ketoconazole, Spironolactone and Cimetidine.

**Renal dysfunction**
Renal disease has no influence on the plasma concentration or LDL-C reduction of Atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary.

**Pregnancy and lactation**
If a woman becomes pregnant while taking Atorvastatin, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Women taking Atorvastatin should not breast-feed because of the potential for adverse reactions in nursing infants.

**Ezetimibe**

**Hepatic dysfunction**
Ezetimibe is not recommended in patients with moderate or severe hepatic insufficiency.

**Renal dysfunction**
No dosage adjustment is recommended in patients with moderate or severe renal insufficiency.

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

**DRUG INTERACTIONS**

**Atorvastatin**
The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of Cyclosporine, Fibric acid derivatives, Niacin, Erythromycin, Azole antifungals. When Atorvastatin is co-administered with antacids, plasma concentration of Atorvastatin is decreased approximately by 35%. Plasma concentration of Atorvastatin was decreased approximately 25% when Colestipol and Atorvastatin were co-administered. When multiple doses of Atorvastatin and Digoxin were co-administered, steady-state plasma Digoxin concentration was increased by approximately 20%. In healthy individuals, plasma concentrations of Atorvastatin increased approximately 40% with co-administration of Erythromycin. Co-administration of Atorvastatin and an oral contraceptive increased AUC values for Norethindrone and Ethinyl-estradiol by approximately 30% and 20% respectively.
Ezetimibe Cholestyramine: Concomitant cholestyramine administration decreases the mean AUC of total Ezetimibe by approximately 55%.

Fibrates: The safety and effectiveness of Ezetimibe administered with fibrates have not been established.

Cyclosporine: Total Ezetimibe level increased 12-fold in one renal transplant patient receiving multiple medications including Ezetimibe.

ADVERSE REACTIONS

Atorvastatin
The most frequent adverse events were constipation, flatulence, abnormally elevated liver function tests, arthralgia, dyspepsia and abdominal pain. Muscle tenderness, rhabdomyolysis and hypersensitivity reactions were also reported.

Ezetimibe
Fatigue, abdominal pain, diarrhea, sinusitis, arthralgia, backpain and coughing were seen in ≥2% of patients treated with Ezetimibe alone.

Co-administration of Atorvastatin and Ezetimibe
In general, adverse experiences were similar between Ezetimibe administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. Frequency of increased transaminases was slightly higher in patients receiving Ezetimibe administered with HMG-CoA reductase inhibitor.

OVERDOSE AND TREATMENT

There is no specific treatment for overdose of FDC. In an event of overdosage, the patient should be treated symptomatically, and supportive measures instituted as required.

DOSAGE AND ADMINISTRATION

The Fixed Dose Combination (FDC) is recommended for oral administration as once daily therapy or as directed by the physician. The patient should be placed on standard cholesterol lowering diet before receiving the FDC and should be continued on this diet during treatment. The FDC can be administered as a single dose at any time of the day with or without food. Therapy should be individualised according to goal of the therapy and response. After initiation of the therapy, lipid levels should be analysed within 2-4 weeks and dose adjusted accordingly.

STORAGE INSTRUCTIONS

Store at a temperature below 30°C, protect from light and moisture. KEEP THE MEDICINE OUT OF REACH OF CHILDREN.
REFERENCES

4. Jim McKenney. Combination therapy for elevated low density lipoprotein cholesterol: The key to coronary artery Disease Risk Reduction. Am J Cardiol 2002; 90(suppl.):8K-20K