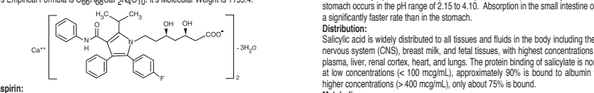
For the use of a Specialist or a Hospital or a Laboratory only 8039188-9093

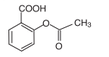
NEW MODLIP-ASG

(Atorvastatin & Aspirin Capsules)

COMPOSITION:
New Modlip-ASG 75 :
Each hard gelatin capsule contains :
Atorvastatin Calcium I.P.
equivalent to Atorvastatin 10 mg
Aspirin I.P. 75 mg
(As enteric coated tablet)
Colours : Titanium Dioxide I.P. & Quinoline Yellow Lake.
Approved colours used in hard gelatin capsule shell.
New Modlip-ASG 150 :
Each hard gelatin capsule contains :
Atorvastatin Calcium I.P.
equivalent to Atorvastatin 10 mg
Aspirin I.P. 150 mg
(As enteric coated tablet)
Colours : Titanium Dioxide I.P. & Quinoline Yellow Lake.
Approved colours used in hard gelatin capsule shell.
DESCRIPTION:
Atorvastatin Calcium:
Atorvastatin calcium is a white to off-white crystalline powder that is slightly soluble in methanol; slightly soluble in ethanol (95 per cent) and very slightly soluble in water. Chemically it is calcium salt of [(*R*,*R*)-2-(4-fluorophenyl)-ß,ä-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoicacid trihydrate.
It's Empirical Formula is $C_{66}H_{68}CaF_2N_4O_{10}$. It's Molecular Weight is 1155.4.



Aspirin:
Aspirin is colourless crystals or a white, crystalline powder; odourless or almost odourless. It is freely soluble in *ethanol* (95 *per cent*); soluble in *chloroform* and in *ether, slightly* soluble in *water*. Chemically it is 2-Acetyloxybenzoic acid. Its empirical formula is $C_9H_8O_4$. It's molecular weight is 180.2.



PHARMACOLOGY:
Pharmacodynamics:
Atorvastatin:
It is lipid modifying agents, HMG-CoA-reductase inhibitors. Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor). Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products. Atorvastatin also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C).
Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.
Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.
Aspirin:
Acetylsalicylic acid (ASA) interferes with the production of prostaglandins in various organs and tissues through acetylation of the enzyme cyclo-oxygenase. The inhibition of platelet aggregation by ASA is due to its ability to interfere with the production of thromboxane A2 within the platelet. Thromboxane A2 is, largely, responsible for the aggregating properties of platelets. Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation may play an equally important role in the evolution of a variety of disease states including cerebrovascular disease, ischemic heart disease and myocardial infarction. Aspirin inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG2 and PGH2 which are precursors of the major platelet-aggregating material, thromboxane A2, which is also a powerful vasoconstrictor. However, aspirin does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets. As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been inactivated, inhibition of platelet aggregation by aspirin thus persists for the life of the platelets. Besides inhibiting the biosynthesis of thromboxane A2 by platelets, aspirin also interferes with the production of prostacyclin (PGI2) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A2 and prostacyclin.This latter compound is one of the most powerfully acting platelet deaggregators and vasodilators and thus it would appear that the interference with the hemostatic processes by aspirin depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of aspirin may be thrombogenic. However, in contrast to platelets, the vascular endothelial cells are able to regenerate cyclo-oxygenase in a relatively short time and therefore therapeutic doses of aspirin are likely to produce a lesser inhibition of the vascular prostacyclin system than of the platelet thromboxane-forming mechanism. In fact, there is no clinical evidence to indicate that high doses of aspirin would result in an increased risk of thromboembolism.
Absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma. Aspirin is bound to plasma proteins and is widely distributed. Plasma aspirin concentrations decline rapidly (half life 15-20 minutes) as plasma salicylate concentrations increase.
Salicylate is mainly eliminated by hepatic metabolism - the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption.
Pharmacokinetics:
Atorvastatin:
Absorption:
Atorvastatin is rapidly absorbed after oral administration with maximum plasma concentrations seen within 1 to 2 hours and extent of absorption increases with the dose. The absolute bioavailability of atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30% which is attributed to presystemic clearance in GI mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, as assessed by Cmax and AUC respectively, LDL-C reduction and HDL-C elevation are similar when atorvastatin is given with and without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following drug administration in the evening compared with morning dosing. However, LDL-C reduction and HDL-C elevation are the same regardless of the time of drug administration.
Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters and > 98% is bound to plasma proteins. A blood plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on rat studies, atorvastatin is likely to be secreted in human milk.
Metabolism : Atorvastatin is extensively metabolized mainly by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. 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.
Excretion : Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, there is no enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin 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 and Conditions:
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.
Paediatric: Pharmacokinetic data in the Paediatric 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); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of atorvastatin should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously.
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 Impairment: 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 whereas in patients with Childs-Pugh B disease, this increase is approximately 16-fold and 11-fold respectively.
SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis. Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.
Aspirin:
Absorption:
Aspirin is well and completely absorbed from the gastrointestinal (GI) tract and is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid seen within 1-2 hours of dosing. The rate of absorption is dependent upon the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. The gastric mucosa is permeable to the non-ionized form of acetylsalicylic acid, which passes through the stomach wall by a passive diffusion process. Optimum absorption of salicylate in the human stomach occurs in the pH range of 2.15 to 4.10. Absorption in the small intestine occurs at a significantly faster rate than in the stomach.
Distribution:
Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues, with highest concentrations seen in plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is non-linear; at low concentrations (< 100 mcg/mL), approximately 90% is bound to albumin while at higher concentrations (> 400 mcg/mL), only about 75% is bound.
Metabolism:
Aspirin is hydrolyzed rapidly by esterases in the gastrointestinal mucosa and the liver to salicylic acid. The half-life of aspirin in the circulation is from 13 to 19 minutes so that the blood level drops quickly after absorption is complete. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites (gentisic acid and other hydroxybenzoic acids).
Excretion:
Excretion of salicylates occurs principally via the kidney, through a combination of glomerular filtration and tubular excretion. Following therapeutic doses, in the form of free salicylic acid, salicyluric acid, as well as phenolic and acyl glucuronides. Salicylate can be detected in the urine shortly after its ingestion but the full dose requires up to 48 hours for complete elimination. The rate of excretion of free salicylate is extremely variable, reported recovery rates in human urine ranging from 10% to 85%, depending largely on urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5% to > 80%. The half-life of salicylic acid is approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 gm), the plasma half-life may be increased to over 20 hours. The elimination of salicylic acid follows zero order pharmacokinetics.
INDICATIONS:
For the treatment of dyslipidemia associated with atherosclerotic arterial disease with risk of myocardial infarction, stroke or peripheral vascular disease.
CONTRAINDICATIONS:
New Modlip-ASG is contraindicated in the following conditions:
1.Hypersensitivity to atorvastatin, aspirin, other salicylates or any other NSAIDs or any of the excipients of this medicinal product.
2. A history of, or active peptic ulceration, haemophilia or other clotting disorders, gout, asthma, urticaria, rhinitis or other evidence of hypersensitivity to aspirin or non steroidal anti-inflammatory drugs.
3.New Modlip-ASG should be avoided in patients with severe renal or hepatic impairment or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
4. New Modlip-ASG should not be used by woman who are pregnant or may become pregnant and in nursing mothers.
WARNINGS AND PRECAUTIONS:
- It is recommended that liver enzyme tests should be performed before starting statin therapy, and as clinically indicated thereafter. The serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing this rare side effects. Patients should notify their health care professional immediately if they have the following symptoms of liver problem: unusual fatigue or weakness, loss of appetite, upper belly pain, dark-colored urine, yellowing of the skin or the whites of the eyes.
- Certain cognitive (brain-related) effects have been reported with statins use. Some patients who are taking the statin containing medicinal products experiences memory loss and confusion. These reports are generally have not been serious and patient's symptoms were reversed by stopping the statin. Patients should immediately contact their healthcare professional if symptoms occur.
- Increase in blood sugar levels (hyperglycemia) have been reported with statin use. The available evidences shows that patients being treated with statins may have a small risk of increased blood sugar levels and of being diagnosed with type 2 diabetes mellitus.

Aspirin : There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. Kawasaki's disease). Aspirin and other NSAIDs may cause salt and water retention and renal failure especially in patients with pre-existing renal impairment.
Caution should be exercised in patients with asthma, asthma and other allergic conditions, bleeding tendencies, significant anaemia, hypoprothrombinemia, impairment of hepatic or renal function and dehydration.
Atorvastatin
Liver effects:
Liver function tests should be performed before the initiation of treatment and thereafter if clinically indicated. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. New Modlip-ASG should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels:
Clinical studies shows patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) shows a higher incidence of hemorrhagic stroke when they are initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.
Skeletal muscle effects:
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdo myolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.
Before the treatment
New Modlip-ASG should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A Creatine kinase (CK) level should be measured before starting New Modlip-ASG treatment in the following situations:
– Renal impairment.
– Hypothyroidism.
– Personal or familial history of hereditary muscular disorders.
– Previous history of muscular toxicity with a statin or fibrate.
– Previous history of liver disease and/or where substantial quantities of alcohol are consumed.
– In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis .
– Situations where an increase in plasma levels may occur.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.
Whilst on treatment
– Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
– If such symptoms occur whilst a patient is receiving treatment with New Modlip-ASG 75/150, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
– If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to 5 x ULN, treatment discontinuation should be considered.
– If symptoms resolve and CK levels return to normal, then re-introduction of New Modlip-ASG may be considered at the lowest dose and with close monitoring.
– New Modlip-ASG must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products
Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, erythromycin, niacin and ezetimibe. If possible, alternative (non -interacting) therapies should be considered instead of these medicinal products. In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the

case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended . The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy.
Paediatric use : New Modlip-ASG should not be used in the patients below 10 years. Developmental safety in the paediatric population has not been established.
Interstitial lung disease: There is a chance of interstitial lung disease with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
USE IN SPECIFIC POPULATIONS
Atorvastatin
Pregnancy
Pregnancy Category X
Atorvastatin is contraindicated in women who are or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. 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. There are no adequate and well-controlled studies of atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity.
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, atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus.
Nursing mothers
It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin treatment should not breastfeed their infants.
Paediatric Use
Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. Doses greater than 20 mg have not been studied in this patient population. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy. Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Clinical efficacy with doses up to 80 mg/day for 1 year has been evaluated in an uncontrolled study of patients with homozygous FH including 8 paediatric patients.
Geriatric Use
Of the 39,828 patients who received atorvastatin in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin should be prescribed with caution in the elderly.
Hepatic Impairment
Atorvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels.
Aspirin
Pregnancy
Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hempslrasis mechanisms, decreased birth weight, and with perinatal mortality.
Labor and Delivery
Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.
Nursing Mothers
Nursing mothers should avoid using aspirin because Salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.
DRUG INTERACTION:
Aspirin
Alcohol and corticosteroids may enhance the effects of aspirin on the gastrointestinal tract. Aspirin may enhance the effects of coumarin anticoagulant, oral hypoglycaemics (of the sulphonylurea type), phenytoin and sodium valproate. Aspirin may increase the risk of bleeding with other antiplatlet drugs such as clopidogrel and ticlopidine The toxicity of methotrexate may be enhanced by concomitant use of aspirin. Aspirin 75mg may antagonise the diuretic effect of spironolactone and may reduce acetazolamide excretion (risk of toxicity). Aspirin increases plasma concentration of zafirlukast. Metoclopramide and domperidone enhance the effect of aspirin (increased rate of absorption). Avoid concomitant administration with mifepristone (theoretical interaction). Aspirin diminishes the action of uricosurics. Aspirin may reduce the efficacy of antihypertensive drugs. Aspirin is pharmaceutically incompatible with iron salts and alkalis. Avoid concomitant administration of antacids and absorbents (excretion of aspirin is increased in alkaline urine whilst kaolin may reduce absorption). New Modlip-ASG should be administered cautiously for such conditions.
Atorvastatin
Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolized by cytochrome P 450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1.Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe.
CYP3A4 inhibitors
Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended. Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.
CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration 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. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.
Transport protein inhibitors
Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin. The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended.
Gemfibrozil / fibric acid derivatives
The use of Fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored.
Ezetimibe
The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.
Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was co-administered withAtorvastatin. However, lipid effects were greater when Atorvastatin and colestipol were co-administered than when either medicinal product was given alone.
Fusidic acid
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.
Effect of atorvastatin on co-administered medicinal products
Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady - state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.
Oral contraceptives
Co-administration of Atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.
Warfarin
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
ADVERSE REACTIONS
Atorvastatin
Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for.
Estimated frequencies of reactions are ranked according to the following convention: common (≥1/100, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥1/10,000, < 1/1,000); very rare (≥1/10,000).
Infections and Infestations:
Common: nasopharyngitis.
Blood and lymphatic system disorders
Rare: thrombocytopenia.
Immune system disorders
Common: allergic reactions.
Very rare: anaphylaxis.
Metabolism and nutrition disorders
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia
Psychiatric disorders
Uncommon: nightmare, insomnia.
Nervous system disorders
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.
Eye disorders
Uncommon: vision blurred.
Rare: visual disturbance.
Ear and labyrinth disorders
Uncommon: tinnitus
Very rare: hearing loss.
Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain, epistaxis.
Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.
Hepatobiliary disorders
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.
Skin and subcutaneous tissue disorders
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.
Reproductive system and breast disorders
Very rare: gynecomastia.
General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.
Investigations
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.
As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose related and were reversible in all patients. Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin -treated patients.
Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.
Nervous system disorders
Common: Headache
Gastrointestinal disorders
Common: Abdominal pain
Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.
Aspirin
Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature
Body as a whole: Fever, hypothermia, thirst.
Cardiovascular: Dysrhythmias, hypotension, tachycardia.
Central nervous system: Agitation, Cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.
Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.
Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, heartburn, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.
Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia., anaemia, purpura, leukopenia.
Dermatologic and hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, , pruritus, skin eruptions, urticaria.
Muculoskeletal: Rhabdomyolysis.
Metabolism: Hypoglycemia (in children), hyperglycemia.
Reproductive: Prolonged pregnancy and labour, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.
Respiratory: Hyperpnea, pulmonary edema, tachypnea.
Special Senses: Hearing loss, vertigo, tinnitus. Patients with higher frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.
Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.
DOSAGE: The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with FDC of Atorvastatin and aspirin. Route of administration is oral. New Modlip-ASG is administered once daily dose but the dosage should not be increased than maximum allowed dose for individual agents. The maximum dose Atorvastatin is 80mg once daily and for Aspirin for long term use is 75 -150 mg daily. In some circumstances a high dose of Aspirin may be appropriate, especially in the short term, and up to 300 mg a day may be used on the advice of a doctor.
OVERDOSE:
Aspirin
Common features of overdose include dizziness, tinnitus, deafness, vasodilation and sweating, nausea and vomiting, headache and mental confusion. If more severe; hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis. Coma, if severe, with cardiovascular collapse and respiratory failure. Hypoglycaemia may be severe in children. Overdosage should be treated initially by aspiration and lavage and a saline purgative such as sodium sulphate, 30g in 250ml of water should be given to promote peristalsis. Otherwise treat as for aspirin poisoning and observe for at least 72 hours to allow for possible delayed reaction from gastro-resistant system. Restoration of acid-base balance may be necessary.
Atorvastatin
Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.
Expiry Date:
Do not use later than the date of expiry.
Storage:
Store below 25°C, protected from light and moisture.
Keep all medicines out of reach of children.
Presentation:
New Modlip-ASG is available in strip of 10 capsules.

torrent

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