For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

DEPLATT AV

1. Generic Name

Atorvastatin and Clopidogrel Tablets

2. Qualitative and quantitative Composition:

DEPLATT AV 10/20

Each Uncoated Bilayered Tablet Contains:

Atorvastatin Calcium I.P. Equivalent to Atorvastatin…….10 mg /20 mg

Clopidogrel Bisulphate I.P. Equivalent to Clopidogrel…….75 mg

Excipients……q.s.

Colours: Ferric Oxide (Red) USP-NF

The excipients used are Microcrystalline cellulose PH 102,Colloidal silicon dioxide, Crospovidone INF 10, Sodium stearyl Fumarate NF, Microcelac 100,Sodium carbonate, croscarmellose sodium NF, sodium lauryl sulfate, col.iron oxide (ferric oxide NF) Red, magnesium stearate

DEPLATT AV 40

Each Uncoated Bilayered Tablet Contains:

Atorvastatin Calcium I.P. Equivalent to Atorvastatin…….40 mg

Clopidogrel Bisulphate I.P. Equivalent to Clopidogrel…….75 mg

Excipients……q.s.

Colours: Ferric Oxide (Red) USP-NF

The excipients used are Microcrystalline cellulose PH 102, Colloidal silicon dioxide, Crospovidone INF 10, Sodium stearyl Fumarate NF, microcrystalline cellulose PH 101, Lactose monohydrate ,Sodium carbonate (Anhydrous), croscarmellose sodium , sodium lauryl sulfate, col.iron oxide (ferric oxide NF) Red, polyvinyl pyrilidone , magnesium stearate.

3. Dosage form and strength

Dosage form: Tablet

Strength: Atorvastatin 10 mg, 20 mg, 40 mg & Clopidogrel 75 mg

4. Clinical particulars

4.1 Therapeutic indication

10 & 20_It is indicated for post coronary intervention and acute syndrome.

40_It is indicated for the treatment of dyslipidemia associated with artherosclerotic arterial disease with risk of myocardial infarction, stroke, or peripheral vascular disease.

4.2 Posology and method of administration

Patients should be placed on an appropriate lipid-lowering diet before receiving Deplatt AV and should continue this diet during treatment. The recommended dosage is one Tablet once daily.

The dose of atorvastatin can be individualized according to baseline LDL-C levels, the goal of therapy and patient response. The usual starting dose is 10mg once daily. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80mg once daily.

The dosage of clopidogrel in unstable angina (UA) / Non-ST-elevated myocardial infarction (NSTEMI) is 75 mg daily after a single loading dose. In patients with STEMI, recent MI, stroke or peripheral artery disease, the recommended dose of clopidogrel is 75 mg once daily.

Avoid using omeprazole or esomeprazole with Deplatt AV. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.

4.3 Contraindications

Atorvastatin:

- with hypersensitivity to the active substance or to any of the excipients of this medication
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- with myopathy
- during pregnancy
- while breast-feeding
- In women of child-bearing potential not using appropriate contraceptive measures.

Clopidogrel:

- Hypersensitivity to the active substance or to any of the excipients
- Severe hepatic impairment
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage

4.4 Special warnings and precautions for use

Atorvastatin:

Liver function tests should be performed before the initiation of treatment and periodically thereafter. 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. Should an increase in ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Muscle effects

Treatment with HMG-CoA reductase inhibitors (statins) has been associated with the onset of myalgia, myopathy, and very rarely rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness or muscle cramps. In such cases creatine kinase (CK) levels should be measured.

Creatine phosphokinase measurement

Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline (>5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Before treatment

As with other statins atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine phosphokinase (CPK) level should be measured before starting 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

In such situations, the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started.

Whilst on treatment

If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK 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 CPK levels are elevated to ≤ 5 times ULN, treatment discontinuation should be considered.

If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.

The risk of myopathy during treatment with Atorvastatin may be increased with concurrent administration of certain other drugs, such as fibrates (e.g. gemfibrozil) and co-administration should only be undertaken with caution.

As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported.

Children aged 10-17 years

In patients aged <18 years efficacy and safety have not been studied for treatment periods>52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

Clopidogrel:

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during treatment. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2inhibitors. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings.

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Recent ischaemic stroke

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged

Renal impairment

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients.

Hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

4.5 Drugs interactions

Atorvastatin:

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased by concurrent use of cyclosporin, fibrates, macrolide antibiotics including erythromycin, azole antifungals or niacin and has very rarely led to rhabdomyolysis and renal insufficiency caused by myoglobinuria. Possible benefits and the risk involved with concurrent treatment must be considered carefully.

Cytochrome P450 3A4 inhibitors: Atorvastatin is metabolised by cytochrome P450 3A4. Interactions can occur during concurrent administration of atorvastatin and a cytochrome P450 3A4 inhibitor (e.g. cyclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Special precaution is required during concurrent administration of atorvastatin and these products because it can result in elevated plasma concentration of atorvastatin.

Erythromycin (500 mg four times a day) or clarithromycin (500 mg twice a day), known cytochrome P450 3A4 inhibitors, resulted in a higher plasma concentration of atorvastatin. When administered concurrently with atorvastatin, clarithromycin caused a 56% increase in the Cmax of atorvastatin and an 80% increase in its AUC.

P-glycoprotein inhibitors: Atorvastatin and its metabolites are substrates of P-glycoprotein. P-glycoprotein inhibitors (e.g. cyclosporin) can increase the bioavailability of atorvastatin.

Itraconazole: Concurrent administration of atorvastatin 40 mg and itraconazole 200 mg a day resulted in a threefold increase in the AUC of atorvastatin.

Protease inhibitors: Concurrent use of atorvastatin and protease inhibitors which are known CYP3A4 inhibitors resulted in an increased plasma concentration of atorvastatin.

Grapefruit juice: Contains one or more CYP3A4 inhibitors and can cause elevation in plasma concentration of medicinal products metabolised by CYP3A4. The AUC for atorvastatin increased by 37% and the AUC of the active orthohydroxy metabolite decreased by 20.4% following intake of 240 ml of grapefruit juice. A large amount of grapefruit juice (exceeding 1.2 l a day for five days) however causes a 2.5-fold increase in the AUC for atorvastatin and a 1.3-fold increase in AUC for the active HMG-Co A reductase inhibitors (atorvastatin and active metabolites). Drinking large amounts of grapefruit juice is therefore not recommended during atorvastatin treatment.

Cytochrome P450 3A4 inducers: The effects of cytochrome P450 3A4 inducers (e.g. rifampicine or phenytoin) on atorvastatin are not known. Possible interactions with other substrates of this isoenzyme are not known but should be considered in case of medicinal products with a narrow therapeutical index, e.g. class III antiarrhythmics, including amiodarone.

Concurrent use of other medicinal products:

Gemfibrozil/fibrates: The risk of atorvastatin induced myopathy can increase during concurrent administration of fibrates. In vitro studies indicate that gemfibrozil inhibits glucuronization of atorvastatin and can therefore possibly cause increased plasma concentration of atorvastatin.

Digoxin: Repeated administration of digoxin and atorvastatin 10 mg at the same time did not influence the steady state plasma concentration of digoxin. Digoxin concentration however increased by 20% during concurrent use of digoxin and atorvastatin 80 mg a day. This interaction can be explained by inhibition of the P-glycoprotein membrane transferring protein. Patients treated with digoxin should be monitored carefully.

Oral contraceptives: Concurrent use of atorvastatin and oral contraceptives increased the concentration of norethisterone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol: Plasma concentration of atorvastatin and its active metabolites decreased (approx. 25%) when colestipol was administered with atorvastatin. However, lipidaemic effects were greater when atorvastatin and colestipol were administered together than when either drug was administered alone.

Antacids: Concurrent administration of atorvastatin and oral antacid liquid formulations containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations by approx. 35%; reduction of LDL-cholesterol was however not altered.

Warfarin: Concurrent use of atorvastatin and warfarin caused a minor decrease in prothrombin time during the first days of treatment but returned to normal within 15 days. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their treatment.

Phenazone: Concurrent use of atorvastatin and phenazone for some time resulted in little or no visible effect on the clearance of phenazone.

Cimetidine: In reported study of interactions between cimetidine and atorvastatin no interaction was seen.

Amlodipine: Concurrent use of atorvastatin 80 mg and amlodipine 10 mg did not influence pharmacokinetic properties of atorvastatin at steady state.

Other medicinal products: In reported clinical studies no clinically, significant interactions were observed when atorvastatin was administered together with antihypertensives or hypoglycemic agents.

Clopidogrel:

Effect of co-administered medicinal products on Clopidogrel

CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

Omeprazole or esomeprazole

Avoid concomitant use of Clopidogrel with omeprazole or esomeprazole. In reported clinical studies, omeprazole was shown to reduce significantly the antiplatelet activity of Clopidogrel when given concomitantly or 12 hours apart. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Clopidogrel. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of Clopidogrel than did omeprazole or esomeprazole

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Coadministration of Clopidogrel and NSAIDs increases the risk of gastrointestinal bleeding.

Warfarin (CYP2C9 Substrates)

Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

However, at high concentrations in vitro, clopidogrel inhibits CYP2C9.

SSRIs and SNRIs

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

Repaglinide (CYP2C8 Substrates)

The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Clopidogrel can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose-adjustment and/or appropriate monitoring.

Concomitant administration of Clopidogrel with repaglinide significantly increases systemic exposures to repaglinide. When concomitant use is required in a patient maintained on clopidogrel, initiate repaglinide at 0.5 mg with each meal and titrate based on blood glucose levels. Do not exceed a total daily dose of 4 mg. If concomitant use of clopidogrel is required in a patient stabilized on higher doses of repaglinide, down titrate the dose of repaglinide based on blood glucose levels to not exceed a total daily dose of 4 mg.

4.6 Use in special populations (such as pregnant women, lactating women, etc.)

Atorvastatin:

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment.

Pregnancy

Atorvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. In reported animals studies have shown toxicity to reproduction.

Maternal treatment with atorvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, Atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Breast-feeding

It is unknown whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. Because of the potential for serious adverse reactions, women taking Atorvastatin should not breast-feed their infants. Atorvastatin is contraindicated during breast-feeding.

Fertility

In reported animal studies atorvastatin had no effect on male or female fertility.

Clopidogrel:

Pregnancy

As no reported clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Reported animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Breast-feeding

It is unknown whether clopidogrel is excreted in human breast milk. Reported animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.

Fertility

Clopidogrel was not shown to alter fertility in reported animal studies.

4.7 Effects on ability to drive and use machines

Atorvastatin and Clopidogrel has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Atorvastatin:

The most commonly expected adverse events are mainly gastrointestinal, including constipation, flatulence, dyspepsia and abdominal pain. They usually ameliorate on continued treatment.

Less than 2% of patients were discontinued from reported clinical trials due to side effects attributed to atorvastatin.

Based on data from reported clinical studies and extensive post-marketing experience, the following table presents the adverse event profile for atorvastatin.

Estimated frequencies of events 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).

Gastrointestinal disorders:

Common: abdominal pain, constipation, flatulence, dyspepsia, nausea, diarrhoea.

Uncommon: anorexia, vomiting.

Blood and lymphatic system disorders:

Uncommon: thrombocytopenia.

Immune system disorders:

Common: allergic reactions.

Very rare: anaphylaxis.

Endocrine disorders:

Uncommon: alopecia, hyperglycaemia, hypoglycaemia, and pancreatitis.

Psychiatric:

Common: insomnia.

Uncommon: amnesia.

Nervous system disorders*:*

Common: headache, dizziness, paraesthaesia, hypoesthesia.

Uncommon: peripheral neuropathy, Very rare: dysgeusia

Eye Disorders:

Very rare: visual disturbance.

Hepato-biliary disorders:

Rare: hepatitis, cholestatic jaundice.

Very rare: hepatic failure

Skin/Appendages:

Common: Skin rash, pruritus. Uncommon: urticaria.

Very rare: angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Ear and Labyrinth Disorders:

Uncommon: tinnitus.

Very rare: hearing loss

Musculoskeletal disorders:

Common: myalgia, arthralgia, back pain, Uncommon: myopathy, muscle cramps.

Rare: myositis, rhabdomyolysis. Very rare: tendon rupture

Reproductive system disorders:

Uncommon: impotence.

Very rare: gynecomastia.

General disorders:

Common: asthenia, chest pain, peripheral oedema. Uncommon: malaise, weight gain.

Investigations

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 phosphokinase (CPK) 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 reported clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Atorvastatin -treated patients.

Clopidogrel:

Blood and the lymphatic system disorders:

Uncommon: Thrombocytopenia, leucopenia, eosinophilia

Rare: Neutropenia, including severe neutropenia, *Very rare:* Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia

Immune system disorders:

Very rare: Serum sickness, anaphylactoid reactions

Psychiatric disorders*:*

Very rare: Hallucinations, confusion

Nervous system disorders*:*

Uncommon: Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness, Very rare Taste disturbances

Eye disorders**:** *Uncommon:* Eye bleeding (conjunctival, ocular, retinal)

Ear and labyrinth disorders: *Rare* Vertigo

Vascular disorders:

Common: Haematoma

Very rare: Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension.

Respiratory, thoracic and mediastinal disorders:

Common Epistaxis, Very rare Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis

Gastrointestinal disorders:

Common Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia

Uncommon Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence

Rare: Retroperitoneal haemorrhage

very rare: Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis

Hepato-biliary disorders:

Common: Bruising

Very rare: Acute liver failure, hepatitis, abnormal liver function test, Skin and subcutaneous tissue disorders

Common: Bruising

Uncommon: Rash, pruritus, skin bleeding (purpura)

Very rare: Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus

Renal and urinary disorders: *Uncommon:* Haematuria, *very rare:* Glomerulonephritis, blood creatinine increased

General disorders and administration site conditions*:*

Common: Bleeding at puncture site

Very rare: Fever

Investigations, Uncommon Bleeding time prolonged, neutrophil count decreased; platelet count decreased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9 Overdose

Atorvastatin:

No specific treatment for atorvastatin overdose is available. In case of an overdose the patient should be treated symptomatically, and supportive measures should be instituted if required. Liver function should be monitored and serum CPK values also. Due to its extensive binding to plasma proteins haemodialysis is not expected to increase atorvastatin clearance significantly.

Clopidogrel:

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation.

Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults or children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Treatment

Give activated charcoal if an adult present within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5. Pharmacological properties

5.1 Mechanism of Action

Atorvastatin:

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts 3-HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides (TG) circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) fractions. TG and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C) and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-cholesterol (HDL-C) are associated with a decreased cardiovascular risk.

In reported animal models, atorvastatin 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; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of reported clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apo A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG and non-HDL-C and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces IDL cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Clopidogrel:

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.

5.2 Pharmacodynamic properties

Atorvastatin:

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

Clopidogrel:

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP. Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Clopidogrel. Repeated doses of 75 mg Clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days. Geriatric Patients Elderly (≥75 years) and young healthy subjects had similar effects on platelet aggregation. Renally-Impaired Patients After repeated doses of 75 mg Clopidogrel per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation. Hepatically-Impaired Patients After repeated doses of 75 mg Clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. Gender In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

5.3 Pharmacokinetic properties

Atorvastatin:

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal (GI) mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by the Cmax and area under curve (AUC), LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution

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

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various betaoxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by CYP450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known

inhibitor of this isozyme. In animals, the orthohydroxy metabolite undergoes further glucuronidation.

Elimination

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric:

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

Pediatric:

Pharmacokinetic data in the pediatric population are not available.

Gender:

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); 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; thus, dose adjustment in patients with renal dysfunction is not necessary.

Hemodialysis:

While no reported 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 Child-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B disease.

Clopidogrel:

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of Food

Clopidogrel can be administered with or without food. In a study in healthy male subjects when Clopidogrel 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC0-24 was unchanged

in the presence of food, while there was a 57% decrease in active metabolite Cmax. Similar results were observed when a Clopidogrel 300 mg loading dose was administered with a high-fat breakfast.

Distribution

Clopidogrel and the main circulating inactive metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable in vitro up to a concentration of 100 mcg/mL.

Metabolism

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The Cmax of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in Cmax and AUC, respectively.

Elimination

Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Atorvastatin:

In a 2-year carcinogenicity reported study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity reported study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies reported in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg

dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

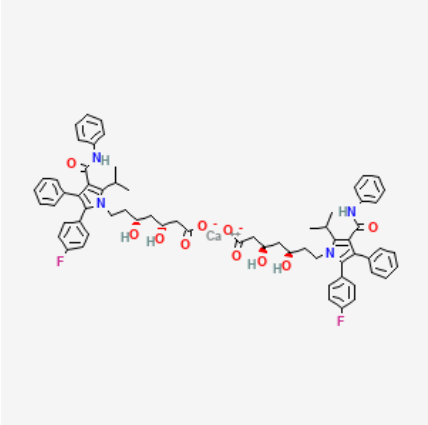
Clopidogrel:

There was no reported evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in four in vitro tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one in vivo test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m2 basis).

7. Description

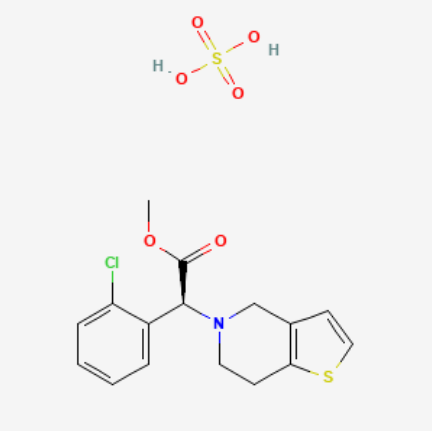
Atorvastatin Calcium

Atorvastatin Calcium is calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoate The empirical formula of atorvastatin calcium is $C_{66}H_{68}CaF_2N_4O_{10}$ and its molecular weight is 1155.3 g/mol. Its structural formula is:



Clopidogrel Bisulphate

Clopidogrel bisulphate, is methyl (2S)-2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c] pyridin-5-yl)acetate; sulfuric acid. The empirical formula of clopidogrel bisulfate is $C_{16}H_{18}ClNO_6S_2$ and its molecular weight is 419.9 gm/mol. The structural formula is as follows:



DEPLATT AV 10/20

DEPLATT AV 10 & 20 is Light Pink & Off White coloured, circular, flat faced, uncoated bilayer tablet having plain on both sides.

The excipients used are microcrystalline cellulose PH 102 , colloidal silicon dioxide ,cros povidone INF 10, sodium stearyl Fumarate NF , microcrystalline cellulose PH 101,Lactose monohydrate, sodium carbonate(Anhydrous), croscarmellose sodium, sodium lauryl sulphate, col. Iron oxide (Ferric oxide NF) red, polyvinyl pyrilidone ,magnesium stearate

DEPLATT AV 40

DEPLATT AV 40 is Light Pink & Off White coloured, circular, flat faced, plain on both sides, uncoated bilayer tablet.

The excipients used are microcrystalline cellulose PH 102 , colloidal silicon dioxide ,cros povidone INF 10, sodium stearyl Fumarate NF , microcrystalline cellulose PH 101,Lactose monohydrate, sodium carbonate(Anhydrous), croscarmellose sodium, sodium lauryl sulphate, col. Iron oxide (Ferric oxide NF) red, polyvinyl pyrilidone ,magnesium stearate

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

DEPLATT AV is available in Strip of 10 tablets

8.4 Storage and handing instructions

Store protected from light & Moisture, at a temperature not exceeding 30°C.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed

- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Manufactured by:

Pure & Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums drugs & phamraceuticals Ltd.)

Plot No-26A,27-30, sector-8A, I.I.E, SIDCUL,

Ranipur, Haridwar-249403, Uttarakhand.

11. Details of permission or license number with date

Mfg. Lic. No.: 31/UA/2013 10 & 20 issued on 07.12.2021 40 issued on 05.11.2022

12. Date of revision

JUL-2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/DEPLATT AV/JUL 2026/02/PI