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

DEPLATT CV 40

1. Generic Name

Atorvastatin, Clopidogrel & Aspirin Capsules

2. Qualitative and quantitative Composition:

Each hard gelatin capsule contains:

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

(As green coloured pellets)

Colours: Tartrazine Supra, Tartrazine Lake & Brilliant Blue Supra, Brilliant Blue Lake.

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

(As two reddish brown coloured film coated tablets, each containing 37.5 mg Clopidogrel Tablets I.P.)

Colours: Ferric Oxide Red USP-NF & Titanium Dioxide I.P.

Aspirin I.P. ……...75mg

(As enteric coated white-coloured pellets)

Approved colours used in capsule shells.

The excipients used are ready to use Pellets of Atorvastatin & Aspirin, Microcrystalline Cellulose, Pregelatinised Starch, Isopropyl Alcohol, Colloidal Silicone Dioxide, Polyethylene Glycol – 6000, Purified Talc Talcum, Dichloromethane, Titanium Dioxide, Hydroxy Propyl Methyl cellulose, Colour Iron Oxide Red, E.G. Caps.

3. Dosage form and strength

Dosage form: Hard gelatin capsules

Strength: Atorvastatin 40 mg, Clopidogrel 75 mg & Aspirin 75 mg

4. Clinical particulars

4.1 Therapeutic indication

In the treatment of patients with PCI (Percutaneous coronary intervention) and myocardial infarction (MI).

4.2 Posology and method of administration

The recommended dosage is once daily or as directed by the Physician. Capsule should be taken orally.
For aspirin not to be used in children below 12 years of age except under medical advice. The dose should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response.
The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

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

Aspirin:

- Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g.certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria), or to any of the excipients.
- Active, or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopeniaor concurrent anticoagulant therapy.
- Patients who are suffering from gout.
- Severe hepatic impairment.
- Severe renal impairment.
- Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).
- Doses >100 mg/day during the third trimester of pregnancy; Methotrexate used at doses >15mg/week.

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-2 inhibitors. 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.

Excipients

Clopidogrel contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

Aspirin:

Aspirin is not suitable for use as an antiinflammatory/analgesic/antipyretic.

Recommended for use in adults and adolescents from 16 years of age. This medicinal product is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's Syndrome in some children.

There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Aspirin is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin is to be used with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn. Acetylsalicylic acid should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid. Aspirin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin reuptake inhibitors and deferasirox.

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin taken at over dosage.

Aspirin should be avoided in late pregnancy and generally during breast feeding.

Aspirin contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Aspirin contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 one 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.

Aspirin:

Contraindicated Combinations

Methotrexate (used at doses >15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin is contraindicated.

Not Recommended Combinations

Uricosuric agents, e.g. probenecid: Salicylates reverse the effect of probenecid. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. coumarin, heparin, warfarin and phenindione:

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet Agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine):

Increased risk of gastrointestinal bleeding

Antidiabetics, e.g. Sulphonylureas:

Salicylics may increase the hypoglycaemic effect of sulphonylureas

Digoxin and Lithium:

Aspirin impairs the renal excretion of lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of lithium is recommended when initiating and terminating treatment with Atorvastatin & Aspirin. Dose adjustment may be necessary.

Diuretics and Antihypertensives:

Aspirin may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other aspirin concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency Diuretics: There is risk of acute renal failure due to decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Carbonic Anhydrase Inhibitors (Acetazolamide):

It may result in severe acidosis and increased central nervous system toxicity.

Systemic Corticosteroids: The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered

Methotrexate (used at doses <15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs:

Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen:

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use

Ciclosporin, Tacrolimus:

Concomitant administration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents.

Valproate:

Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin (an antiepileptic):

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol:

Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Metamizole:

Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients 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 film-coated capsule.

Fertility

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

Aspirin:

Pregnancy

Low doses (up to 100 mg/day):

Reported clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100- 500 mg/day:

There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased preand post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- Inhibition of uterine contractions resulting in delayed or prolonged labour
- Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Lactation

As aspirin is excreted in breast milk, Aspirin should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant.

4.7 Effects on ability to drive and use machines

Not Applicable

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, 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 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.

Aspirin:

Blood and lymphatic system disorders:

Common: Increased bleeding tendencies.

Rare: Thrombocytopenia, granulocytosis, aplastic anaemia.

Not known: Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).

Immune system disorders:

Rare: Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.

Metabolism and digestive system disorders:

Not known: Hyperuricemia.

Nervous system disorders:

Rare: Intracranial haemorrhage

Not known: Headache, vertigo

Ear and labyrinth disorders:

Not known: Reduced hearing ability; tinnitus

Vascular disorders:

Rare: Hemorrhagic vasculitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: Rhinitis, dyspnoea.

Rare: Bronchospasm, asthma attacks

Reproductive system and mammary disorders:

Rare: Menorrhagia

Gastrointestinal disorders:

Common: Dyspepsia.

Rare: Severe gastrointestinal haemorrhage, nausea, vomiting.

Not known: Gastric or duodenal ulcers and perforation, diarrhoea

Hepatobiliary disorders:

Not known: Hepatic insufficiency

Skin and subcutaneous tissue disorders:

Uncommon: Urticaria.

Rare: Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.

Renal and urinary tract disorders:

Not known: Impaired renal function, salt and water retention

Reporting of suspected adverse reactions

Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Atorvastatin:

No specific treatment for Atacor 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.

Aspirin:

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

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.

Aspirin:

Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclooxygenase via acetylation. Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet-aggregating factor thromboxane A2.

Non-acetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation. At higher doses, aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated.

It is this non-specific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation.

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.

Aspirin:

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin.

Aspirin inhibits platelet aggregation. Blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions. Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption. Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Reported experimental data suggest that Ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of Ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin (81mg) a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred.

However, the limitations of these reported data and the uncertainties regarding extrapolation of ex vivo, data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.3 Pharmacokinetic properties

Atorvastatin & Aspirin:

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).

Aspirin:

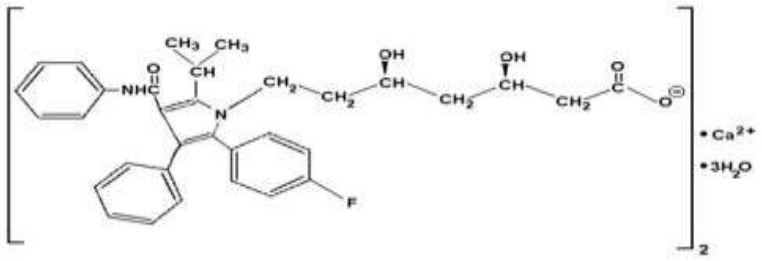
The reported nonclinical safety profile of acetylsalicylic acid is well documented.

In reported experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications. Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

7 Description

Atorvastatin Calcium

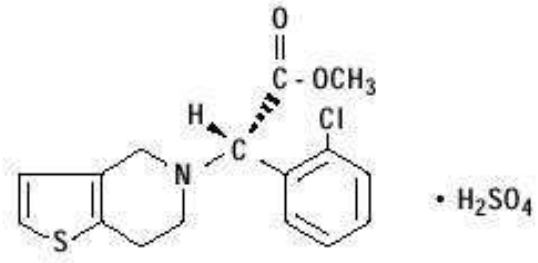
Atorvastatin Calcium is calcium salt of (βR,8R)-2-(4-fluorophenyl)-α,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder. It is freely soluble in methanol; slightly soluble in ethanol (95%) and very slightly soluble in water.

Clopidogrel Bisulphate

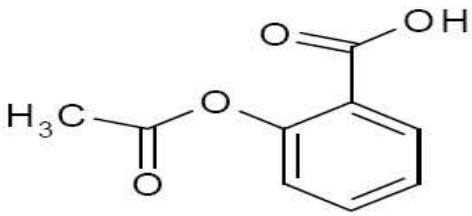
Clopidogrel bisulphate, a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. Chemically it is methyl (+) -(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5-(4H) acetate sulfate. The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \bullet H_2SO_4$ and its molecular weight is 419.9.The structural formula is as follows:



Clopidogrel bisulphate IP is a white to off-white powder. It is freely soluble in methanol; practically insoluble in ether.

Aspirin

The antiplatelet agent aspirin (acetylsalicylic acid) is chemically known as benzoic acid, 2-(acetyloxy)-, The empirical formula of aspirin is $C_9H_8O_4$ and its molecular weight is 180.2 and has the following structural formula:



Aspirin IP is colourless crystals or a white, crystalline powder; odourless or almost odourless. It is freely soluble in ethanol (95 per cent) and soluble in chloroform and in ether; slightly soluble in water.

Atorvastatin, Clopidogrel & Aspirin Capsules are Scarlet Cap/Scarlet Body coloured, size"00" hard gelatin capsule, containing white and green coloured pellets and two reddish coloured, round, biconvex, film coated tablet, plain on both sides.

The excipients used are ready to use Pellets of Atorvastatin & Aspirin, Microcrystalline Cellulose, Pregelatinised Starch, Isopropyl Alcohol, Colloidal Silicone Dioxide, Polyethylene Glycol – 6000, Purified Talc Talcum, Dichloromethane, Titanium Dioxide, Hydroxy Propyl Methyl cellulose, Colour Iron Oxide Red, E.G. Caps.

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 CV 40 is available in Blister Strip of 10 Capsules.

8.4 Storage and handing instructions

- Store in a dry place at a temperature not exceeding 25°C. Protect from light.
- Keep all medicines out of reach of children.
- Not to be used for children below 12 years of age except under medical advice.

• Important: Do not lake this product during the last three months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problem to both mother and child.

9 Patient Counselling Information

Package leaflet: Information for the user

DEPLATT CV 40

Atorvastatin, Clopidogrel & Aspirin Capsules

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

What is in this leaflet

9.1 What is DEPLATT CV 40 and what it is used for

DEPLATT CV 40 is a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. DEPLATT CV 40 is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone. DEPLATT CV 40 can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

• age, smoking, high blood pressure, low HDL-C, heart disease in the family. DEPLATT CV 40 can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

• eye problems, kidney problems, smoking, or high blood pressure. DEPLATT CV 40 starts to work in about 2 weeks.

Aspirin belongs to a group of medicines called antiplatelet drugs. Platelets are very small structures in blood, smaller than red or white blood cells, which clump together during blood clotting. By preventing this clumping, antiplatelet drugs reduce the chances of blood clots forming (a process called thrombosis).

9.2 What you need to know before you take DEPLATT CV 40

Do not take DEPLATT CV 40

• are pregnant or think you may be pregnant or are planning to become pregnant. DEPLATT CV 40 may harm your unborn baby. If you get pregnant, stop taking DEPLATT CV 40 and call your doctor right away.

• are breast feeding. DEPLATT CV 40 can pass into your breast milk and may harm your baby. have liver problems.

• are allergic to DEPLATT CV 40 or any of its ingredients. The active ingredient is atorvastatin.

• See the end of this leaflet for a complete list of ingredients in DEPLATT CV 40 and has not been studied in children under 10 years of age.

• are allergic to ASA, salicylates, non-steroidal anti- inflammatory drugs (NSAIDs)/pain relievers/fever reducers, or other ingredients in the product

• have an ulcer, history of ulcers or are prone to bleeding

• have active or severe liver or kidney disease or congestive heart failure

• have a history of asthma caused by salicylates or other NSAIDs

• are using methotrexate at doses of 15mg/week or more

• are in the last trimester of pregnancy because it may cause problems in the unborn child or coplications during delivery**.**

What Should I Avoid While Taking DEPLATT CV 40?

Talk to your doctor before you start any new medicines. This includes prescription and nonprescription medicines, vitamins, and herbal supplements. DEPLATT CV 40 and certain other medicines can interact causing serious side effects.

Do not get pregnant. If you get pregnant, stop taking DEPLATT CV 40 right away and call your doctor.

9.3 How to take DEPLATT CV 40

Take DEPLATT CV 40 exactly as prescribed by your doctor. Do not change your dose or stop DEPLATT CV 40 without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with DEPLATT CV 40. Your dose of DEPLATT CV 40 may be changed based on these blood test results.

Take DEPLATT CV 40 each day at any time of day at about the same time each day. DEPLATT CV 40 can be taken with or without food.

Your doctor should start you on a low-fat diet before giving you DEPLATT CV 40. Stay on this low-fat diet when you take DEPLATT CV 40.

If you take more DEPLATT CV 40 than you should:

If you take too much DEPLATT CV 40 or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

If you forget to take DEPLATT CV 40

If you miss a dose of DEPLATT CV 40, take it as soon as you remember. Do not take DEPLATT CV 40 if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of DEPLATT CV 40 at the same time.

If you stop taking DEPLATT CV 40

Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

DEPLATT CV 40 can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or DEPLATT CV 40 is stopped. These serious side effects include:

• ***Muscle problems.***

DEPLATT CV 40 can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with DEPLATT CV 40.

• ***Liver problems.***

DEPLATT CV 40 can cause liver problems. Your doctor may do blood tests to check your liver before you start taking DEPLATT CV 40, and while you take it. Call your doctor right away if you have:

• muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.

• allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.

• nausea and vomiting.

• passing brown or dark colored urine.

• you feel more tired than usual

• your skin and whites of your eyes get yellow.

• stomach pain.

• allergic skin reactions. In clinical studies, patients reported the following common side effects while taking DEPLATT CV 40: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with DEPLATT CV 40: tiredness, and tendon problems. Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away. These are not all the side effects of DEPLATT CV 40. Ask your doctor or pharmacist for a complete list.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store DEPLATT CV 40

- Store in a dry place at a temperature not exceeding 25°C. Protect from light.
- Keep all medicines out of reach of children.
- Not to be used for children below 12 years of age except under medical advice.

Important: Do not lake this product during the last three months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problem to both mother and child.

9.6 Contents of the pack and other information

Each hard gelatin capsule contains Atorvastatin Calcium, Clopidogrel and Aspirin

The excipients used are ready to use Pellets of Atorvastatin & Aspirin, Microcrystalline Cellulose, Pregelatinised Starch, Isopropyl Alcohol, Colloidal Silicone Dioxide, Polyethylene Glycol – 6000, Purified Talc Talcum, Dichloromethane, Titanium Dioxide, Hydroxy Propyl Methyl cellulose, Colour Iron Oxide Red, E.G. Caps.

DEPLATT CV 40 is available in Blister Strip of 10 Capsules.

10 Details of manufacturer

Manufactured in India by :

Windlas Biotech Limited (Plant-2),

Khasra No. 141 to 143 & 145,

Mohabewala Industrial Area, Dehradun-248110, Uttarakhand

11 Details of permission or licence number with date

Mfg. Lic. No.: 34/UA/2013 issued on 05.10.2021

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ DEPLATT CV 40, 75, 75mg/NOV-21/01/PI