Atorlip®
Atorvastatin

FORMS AND PRESENTATION
Atorlip® 10: Film Coated tablets: Box of 30.
Atorlip® 20: Film Coated tablets: Box of 30.
Atorlip® 40: Film Coated tablets: Box of 30.
COMPOSITION
Atorlip® 10: Each film coated tablet contains Atorvastatin Calcium eq. to Atorvastatin 10mg.
Atorlip® 20: Each film coated tablet contains Atorvastatin Calcium eq. to Atorvastatin 20mg.
Atorlip® 40: Each film coated tablet contains Atorvastatin Calcium eq. to Atorvastatin 40mg.
Excipients: Lactose monohydrate, Microcrystalline Cellulose PH102, Calcium carbonate Granules, Croscarmellose sodium, Crospovidone 100, Colloidal silicon dioxide 200, Magnesium stearate, polyvinyl alcohol, Titanium dioxide, polyethylene glycol, Talc.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Lipid modifying agents, HMG-CoA-reductase inhibitors
ATC code: C10AA05
Atorlip® is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).
Atorlip® lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.
Atorlip® reduces LDL production and the number of LDL particles. Atorlip® produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorlip® is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.
Pharmacokinetic properties
Absorption
Atorlip® 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. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution
Mean volume of distribution of atorvastatin is approximately 381 l. Atorlip® is ≥ 98% bound to plasma proteins.

Biotransformation
Atorlip® is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.
Elimination
Atorlip® is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special populations
Elderly
Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
Pediatric
Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.
Gender
Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
Renal impairment
Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
Hepatic impairment
Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

INDICATIONS
Hypercholesterolaemia
Atorlip® is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

Atorlip® is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Prevention of cardiovascular disease
Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

CONTRAINDICATIONS
Atorlip® is contraindicated in patients:
-with hypersensitivity to the active substance or to any of the excipients of this product.
-with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
-during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures

PRECAUTIONS
Liver effects
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 transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorlip® is recommended.
Atorlip® should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.
Skeletal muscle effects
Atorlip®, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.
Before the treatment
Atorlip® should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions and special populations including genetic subpopulations.
In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.
If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Whilst on treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorlip® must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Ability to drive and use machines
Atorlip® has negligible influence on the ability to drive and use machines.

PREGNANCY AND LACTATION
Atorlip® 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.
Atorlip® is contraindicated during breastfeeding. It is not known 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 Atorlip® should not breast-feed their infants.
DRUG INTERACTIONS
CYP3A4 inhibitors
Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if

possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended.
Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors.
CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.
Transport protein inhibitors
Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended.
Gemfibrozil / fibric acid derivatives
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored.
Ezetimibe
The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.
Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was co-administered with Atorlip®. However, lipid effects were greater when Atorlip® and colestipol were co-administered than when either medicinal product was given alone.
Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.
Colchicine
Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.
Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.
Oral contraceptives
Co-administration of Atorlip® with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.
Warfarin
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs.

ADVERSE EFFECTS
Estimated frequencies of reactions are ranked according to the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (≤ 1/10,000), not known (cannot be estimated from the available data).
Infections and infestations: Common: nasopharyngitis.
Blood and lymphatic system disorders: Rare: thrombocytopenia.
Immune system disorders: Common: allergic reaction. Very rare: anaphylaxis.
Metabolism and nutrition disorders: Common: hyperglycaemia. Uncommon: hypoglycaemia, weight gain, anorexia
Psychiatric disorders: Uncommon: nightmare, insomnia.
Nervous system disorders: Common: headache. Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia. Rare: peripheral neuropathy.
Eye disorders: Uncommon: vision blurred. Rare: visual disturbance.
Ear and labyrinth disorders: Uncommon: tinnitus. Very rare: hearing loss.
Respiratory, thoracic and mediastinal disorders: Common: pharyngolaryngeal pain, epistaxis.
Gastrointestinal disorders: Common: constipation, flatulence, dyspepsia, nausea, diarrhoea. Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.
Hepatobiliary disorders: Uncommon: hepatitis. Rare: cholestasis. Very rare: hepatic failure.
Skin and subcutaneous tissue disorders: Uncommon: urticaria, skin rash, pruritus, alopecia. Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders: Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain. Uncommon: neck pain, muscle fatigue. Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture. Not known: immune-mediated necrotizing myopathy.
Reproductive system and breast disorders: Very rare: gynecomastia.
General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.
Investigations: Common: liver function test abnormal, blood creatine kinase increased. Uncommon: white blood cells urine positive.
Pediatric Population.
Paediatric patients aged from 10 to 17 years of age treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections.
Based on the data available, the frequency, type and severity of adverse reactions in children is similar to adults.

The following adverse events have been reported with some statins:
Sexual dysfunction, Depression, Exceptional cases of interstitial lung disease, especially with long term therapy, Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

DOSAGE AND ADMINISTRATION
The patient should be placed on a standard cholesterol-lowering diet before receiving Atorlip® and should continue on this diet during treatment with Atorlip®.
The dose should be individualised 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.
Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with Atorlip® 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.
Heterozygous familial hypercholesterolaemia
Patients should be started with Atorlip® 10 mg daily. Doses should be individualized and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.
Homozygous familial hypercholesterolaemia
Only limited data are available. The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
Prevention of cardiovascular disease
In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.
Patients with hepatic impairment
Atorlip® should be used with caution in patients with hepatic impairment. Atorlip® is contraindicated in patients with active liver disease.
Use in the elderly
Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.
Pediatric use
Hypercholesterolemia:
Pediatric use should only be carried out by physicians experienced in the treatment of pediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.
For patients with Heterozygous Familial Hypercholesterolemia aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80 mg daily is supported by study data in adults and by limited clinical data from studies in children with Heterozygous Familial Hypercholesterolemia.
Method of administration
Atorlip® is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.

OVERDOSAGE
Specific treatment is not available for Atorlip® overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

STORAGE CONDITIONS
Store below 25°C.
Keep in original pack in intact conditions.

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Manufactured by:
Benta S.A.L. - Lebanon
BPI

Trademark Owner
Abbott Healthcare Products B.V. Netherlands
Abbott

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists