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

# MODLIP F
## (Atorvastatin and Fenofibrate Tablets)

## COMPOSITION
FDC of Atorvastatin and Fenofibrate is a fixed-dose combination of 10 mg atorvastatin and fenofibrate 160 mg

Each film coated tablet contains:
Atorvastatin Calcium I.P.
equivalent to Atorvastatin 10 mg
Fenofibrate I.P. (Micronized) 160 mg
Colour: Titanium Dioxide I.P.

## DOSAGE FORM
Film coated tablet

## INDICATIONS
**Combined hyperlipidemia**
FDC of Atorvastatin and Fenofibrate is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, apo B, and TG levels and to increase HDL-C in these patients. Lipid altering agents should be used in addition to diet restricted in saturated fat and cholesterol only when the response to diet and other non-pharmacological measures has been inadequate [see National Cholesterol Education Program (NCEP) Guidelines, summarized in the table below].

| **Risk category** | **LDL goal (mg/dl)** | **LDL level at which to consider drug therapy (mg/dl)** |
|---|---|---|
| CHD or CHD risk equivalents* (10-yr risk > 20 %) | < 100 | ≥ 130 (100-129: drug optional) |
| 2+ risk factors ** (10-yr risk < 20%) | < 130 | 10-yr risk 10%-20%: >130<br>10-yr risk <10% :> 160 |
| 0-1 risk factor ** | < 160 | ≥ 190 (160-189; LDL-lowering drug optional) |

*Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
** Other risk factors for coronary heart disease (CHD) include: age (males > 45 years, females L 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension, confirmed HDL-C M 40 mg/dL (M 0.91 mmol/L); and diabetes mellitus. Subtract 1 risk factor if HDL-C is L 60 mg/dL ( L 1.6 mmol/L) After the LDL-cholesterol goal has been achieved, if the triglyceride level is still L 200 mg/dl, non HDL-cholesterol (total cholesterol minus HDL cholesterol) becomes a secondary target of therapy. Non HDL-cholesterol goals are set 30 mg/dl higher than LDL-cholesterol goals for each risk category.

## POSOLOGY AND METHOD OF ADMINISTRATION

One tablet once a day or as directed by physician.

**Atorvastatin**

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

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.

combined (mixed) hyperlipidaemia
The majority of patients are controlled with atorvastatin 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.

Patients with renal impairment
No adjustment of dose is required.

Patients with hepatic impairment
Atorvastatin should be used with caution in patients with hepatic impairment. Atorvastatin 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.

Method of administration
Atorvastatin 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.

**Fenofibrate**

Dietary measures initiated before therapy should be continued. Response to therapy should be monitored by determination of serum lipid values. If an adequate response has not been achieved after several months (e.g. 3 months) complementary or different therapeutic measures should be considered.

*Posology:*

*Adults:*
The recommended dose is one tablet containing 160 mg fenofibrate taken once daily.

*Special populations*
Geriatric populations:
In elderly patients, without renal impairment, the usual adult dose is recommended.

Renal impairment:
Dosage reduction is required in patients with renal impairment. In mild to moderate chronic kidney disease, start with one capsule of 100 mg standard or 67 mg micronized once daily.

In patients with severe chronic kidney disease, fenofibrate is not recommended.

Hepatic impairment:
Fenofibrate 160 mg is not recommended for use in patients with hepatic impairment due to the lack of data.
Paediatric population:
The safety and efficacy of fenofibrate in children and adolescents younger than 18 years has not been established. No data are available. Therefore, the use of fenofibrate is not recommended in paediatric subjects under 18 years.

Method of administration:
Tablet should be swallowed whole during a meal.

**CONTRAINDICATIONS**
It is contraindicated in patients:

- With hypersensitivity to the active substance or to any of the excipients
- With active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- During pregnancy, while breastfeeding and in women of childbearing potential not using appropriate contraceptive measures
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality
- Known gallbladder disease
- Severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 $m^2$)
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia.
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**
**Atorvastatin**
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 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.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a posthoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry.

For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment Skeletal muscle effects Atorvastatin, like other HMGCoA 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.

There have been very rare reports of an immune mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

*Before the treatment*
Atorvastatin should be prescribed with caution in patients with predisposing 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.

*Creatine kinase measurement*

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results. Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis
is diagnosed or suspected.

Concomitant treatment with other medicinal products
Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, boceprevir, erythromycin, niacin,

ezetimibe, telaprevir, or the combination of tipranavir/ritonavir. If possible, alternative (noninteracting) therapies should be considered instead of these medicinal products.

In cases where coadministration of these medicinal products with atorvastatin is necessary, the benefit and the risk ofconcurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended Atorvastatin must not be coadministered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment.

In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination.

The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be reintroduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for coadministration of Atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Paediatric population
No clinically significant effect on growth and sexual maturation was observed in a 3year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight 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. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

**Fenofibrate**
Secondary causes of hyperlipidemia:
Secondary cause of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease or alcoholism should be adequately treated before fenofibrate therapy is considered. Secondary cause of hypercholesterolemia related to pharmacological treatment can be seen with diuretics,

βblocking agents, estrogens, progestogens, combined oral contraceptives, immunosuppressive agents and protease inhibitors.
In these cases it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by these therapeutic agents).

Liver function:

As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and thereafter periodically.

Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.

Pancreas:
Pancreatitis has been reported in patients taking fenofibrate (see sections Contraindications and Undesirable effects). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Muscle:
Muscle toxicity, including rare cases of rhabdomyolysis, with or without renal failure, has been reported with administration of fibrates and other lipid lowering agents. The incidence of this disorder increases in case of hypoalbuminaemia and previous renal insufficiency. Patients with predisposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the upper normal range). In such cases treatment with fenofibrate should be stopped.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMGCoA reductase inhibitor, especially in case of pre-existing muscular disease. Consequently, the coprescription of fenofibrate with HMGCoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and with a close monitoring of potential muscle toxicity.

Renal function:
Fenofibrate 160 mg is contraindicated in severe renal impairment Fenofibrate 160 mg should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated glomerular filtration rate is 30 to 59 mL/min/1.73 $m^2$

Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or coadministered with statins.

Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment.

During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 µmol/L with coadministered fenofibrate and simvastatin versus 4.4% with statin monotherapy. 0.3% of patients receiving coadministration had clinically relevant increases in creatinine to values > 200 µmol/Treatment should be interrupted when creatinine level is 50% above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter excipients:

**DRUG-INTERACTION**

**Atorvastatin**

Effect of coadministered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1.

Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe *CYP3A4 inhibitors* Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Coadministration 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 coadministration 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 (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and coadministration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

*CYP3A4 inducers*

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous

coadministration 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 (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended
(see Table 1).

*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 (ratio of atorvastatin concentration: 0.74) when colestipol was coadministered with Atorvastatin. However, lipid effects were greater when Atorvastatin and colestipol were coadministered 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 coadministered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine. Effect of atorvastatin on coadministered medicinal products

*Digoxin*
When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steadystate digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

*Oral contraceptives*
Coadministration of Atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

*Warfarin*
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment.

Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

Drug Interactions

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

| Co-administered medicinal product and dosing regimen | Atorvastatin | | |
|---|---|---|---|
| | Dose (mg) | Ratio of AUC[&] | Clinical Recommendation[#] |
| Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21) | 40 mg on day 1, 10 mg on day 20 | 9.4 | In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended. |
| Telaprevir 750 mg q8h, 10 days | 20 mg, SD | 7.9 | |
| Ciclosporin 5.2 mg/kg/day, stable dose | 10 mg OD for 28 days | 8.7 | |
| Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days | 20 mg OD for 4 days | 5.9 | In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended. |
| Clarithromycin 500 mg BID, 9 days | 80 mg OD for 8 days | 4.5 | |
| Saquinavir 400 mg BID/ Ritonavir (300 mg BID from | 40 mg OD for 4 days | 3.9 | In cases where co-administration with |

| | | | |
|---|---|---|---|
| days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing | | | atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended. |
| Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days | 10 mg OD for 4 days | 3.4 | |
| Itraconazole 200 mg OD, 4 days | 40 mg SD | 3.3 | |
| Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days | 10 mg OD for 4 days | 2.5 | |
| Fosamprenavir 1400 mg BID, 14 days | 10 mg OD for 4 days | 2.3 | |
| Nelfinavir 1250 mg BID, 14 days | 10 mg OD for 28 days | 1.74 | No specific recommendation. |
| Grapefruit Juice, 240 mL OD * | 40 mg, SD | 1.37 | Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended. |
| Diltiazem 240 mg OD, 28 days | 40 mg, SD | 1.51 | After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended. |
| Erythromycin 500 mg QID, 7 days | 10 mg, SD | 1.33 | Lower maximum dose and clinical monitoring of these patients is recommended. |
| Amlodipine 10 mg, single dose | 80 mg, SD | 1.18 | No specific recommendation. |
| Cimetidine 300 mg QID, 2 weeks | 10 mg OD for 2 weeks | 1.00 | No specific recommendation. |
| Colestipol 10 g BID, 28 weeks | 40 mg OD for 28 weeks | 0.74** | No specific recommendation |
| Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 17 days | 10 mg OD for 15 days | 0.66 | No specific recommendation. |
| Efavirenz 600 mg OD, 14 days | 10 mg for 3 days | 0.59 | No specific recommendation. |
| Rifampin 600 mg OD, 7 days (co-administered) | 40 mg SD | 1.12 | If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring. |
| Rifampin 600 mg OD, 5 days (doses separated) | 40 mg SD | 0.20 | |
| Gemfibrozil 600 mg BID, 7 days | 40 mg SD | 1.35 | Lower starting dose and clinical monitoring of these patients is recommended. |

| | | | |
|---|---|---|---|
| Fenofibrate 160 mg OD, 7 days | 40 mg SD | 1.03 | Lower starting dose and clinical monitoring of these patients is recommended. |
| Boceprevir 800 mg TID, 7 days | 40 mg SD | 2.3 | Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir. |

[&] Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

[#] See sections drug interaction and warning and precaution for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold.
** Ratio based on a single sample taken 8-16 h post dose.

OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily.

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

| Atorvastatin and dosing regimen | Co-administered medicinal product | | |
|---|---|---|---|
| | Medicinal product/Dose (mg) | Ratio of AUC[&] | Clinical Recommendation |
| 80 mg OD for 10 days | Digoxin 0.25 mg OD, 20 days | 1.15 | Patients taking digoxin should be monitored appropriately. |
| 40 mg OD for 22 days | Oral contraceptive OD, 2 months<br>- norethindrone 1 mg<br>-ethinyl estradiol 35 µg | 1.28<br>1.19 | No specific recommendation. |
| 80 mg OD for 15 days | * Phenazone, 600 mg SD | 1.03 | No specific recommendation. |
| 10 mg, SD | Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days | 1.08 | No specific recommendation. |
| 10 mg, OD for 4 days | Fosamprenavir 1400 mg BID, 14 days | 0.73 | No specific recommendation. |

| | | | |
|---|---|---|---|
| 10 mg OD for 4 days | Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days | 0.99 | No specific recommendation. |

[&] Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

OD = once daily; SD = single dose; BID = twice daily.

**Fenofibrate**

Oral anticoagulants:

Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

Cyclosporin:

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMGCoA reductase inhibitors and other fibrates:

The risk of serious muscle toxicity is increased if a fibrate is used concomitantly with HMGCoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.

Glitazones:

Some cases of reversible paradoxical reduction of HDL cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL cholesterol if one of these components is added to the other and stopping of either therapy if HDL cholesterol is too low.

Cytochrome P450 enzymes:

*In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild to moderate inhibitors of CYP2C9 at therapeutic concentrations.

Patients coadministered

fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

## FERTILITY, PREGNANCY AND LACTATION

**Atorvastatin**

Women of childbearing potential Women of childbearing 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 HMGCoA reductase inhibitors have been received. Studies in animals have shown toxicity to reproduction maternal treatment with atorvastatin may reduce the fetal 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 Breastfeeding 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 breastfeed their infants. Atorvastatin is contraindicated during breastfeeding

Fertility

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

**Fenofibrate**

Pregnancy: There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity. The potential risk for humans is unknown. Therefore, Fenofibrate 160 mg film coated tablet should only be used during pregnancy after a careful benefit/risk assessment.

Lactation: It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore, fenofibrate should not be used during breastfeeding.

Fertility: Reversible effects on fertility have been observed in animals (see section 5.3). There are no clinical data on fertility from the use of Fenofibrate 160 mg.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

**Atorvastatin**

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

**Fenofibrate**

It has no or negligible influence on the ability to drive and use machines.

## UNDESIRABLE EFFECTS

**Atorvastatin**

In the atorvastatin placebo controlled clinical trial database of 16,066 (8755 Atorvastatin vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.
Based on data from clinical studies and extensive postmarketing experience, the following table presents the adverse reaction profile for Atorvastatin.

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 reactions.
Very rare: anaphylaxis.
Metabolism and nutrition disorders
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia.
Psychiatric disorders
Uncommon: nightmare, insomnia.
Nervous system disorders
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.
Eye disorders
Uncommon: vision blurred.
Rare: visual disturbance.
Ear and labyrinth disorders
Uncommon: tinnitus.
Very rare: hearing loss.
Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain, epistaxis.
Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.
Hepatobiliary disorders
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.
Skin and subcutaneous tissue disorders
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens Johnson
syndrome and toxic
epidermal necrolysis.
Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.

Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.
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.
As with other HMGCoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on Atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Atorvastatin, similar to other HMGCoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Atorvastatin treated Patients.

Paediatric 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. No clinically significant effect on growth and sexual maturation was observed in a 3year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in paediatric patients was similar to the known safety profile of atorvastatin in adult patients.

The clinical safety database includes safety data for 520 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 121 patients were in the age range of 6 to 9, and 392 patients were in the age range of 10 to 17. 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).

**Fenofibrate**
The most commonly reported ADRs during fenofibrate therapy are digestive, gastric or intestinal disorders. The following undesirable effects have been observed during placebo controlled clinical trials (n=2344) and postmarketing with the below indicated frequencies:

* In the FIELD study, a randomized placebo controlled trial performed in 9,795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed

in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022) and a statistically nonsignificant increase in deep vein thromboses (placebo: 1.0% [48/4,900 patients] versus fenofibrate 1.4% [67/4,895 patients] ; p = 0.074).
** In the FIELD study, the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 µmol/L, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance of this is not clear.

**OVERDOSE**

**Atorvastatin**

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

**Fenofibrate**

Only anecdotal cases of fenofibrate overdosage have been received. In the majority of cases no overdose symptoms were reported.
No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis

**PHARMACOLOGICAL PROPERTIES**

**Atorvastatin**

Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG CoAreductase inhibitors, ATC code: C10AA05 Atorvastatin is a selective, competitive inhibitor of HMGCoA reductase, the rate limiting enzyme responsible for the conversion of 3hydroxy3methylglutarylcoenzyme 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 catabolised primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMGCoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles.

Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDLC in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of totalC (30% 46%),
LDLC (41% 61%),
apolipoprotein B (34% 50%),

and triglycerides (14% 33%)

while producing variable increases in HDLC and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin dependent diabetes mellitus. Reductions in totalC, LDLC, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Homozygous familial hypercholesterolaemia in a multicenter 8-week open label compassionate use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDLC was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was 0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for revascularisation, non-fatal myocardial infarction, coronary death) was not investigated in this study.

In the atorvastatin group, LDLC was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dl ± 30) from baseline 3.89 mmol/L ± 0.7 (150 mg/dl ± 28) and in the pravastatin group, LDLC was reduced to a mean of 2.85 mmol/L ± 0.7 (110mg/dl ± 26) from baseline 3.89 mmol/L ± 0.7 (150 mg/dl ± 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: 18.4%, p<0.0001), mean TG levels by 20% (pravastatin: 6.8%,p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: 22.0%,p<0.0001).

Atorvastatin increased mean HDLC by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001). Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.
The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown. Acute coronary syndrome in the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Qwave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks.

Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in rehospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

The safety profile of atorvastatin in the MIRACL study was consistent with what is described

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and nonfatal coronary heart disease was assessed in a randomised, double-blind, placebo controlled study, the Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOTLLA).

Patients were hypertensive, 4079 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/L (251 mg/dl). All patients had at least 3 of the predefined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDLC>6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event. Patients were treated with antihypertensive therapy (either amlodipine or atenolol based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

The absolute and relative risk reduction effect of atorvastatin was as follows:

| Event | Relative Risk Reduction (%) | No. of Events (Atorvastatin vs Placebo) | Absolute Risk Reduction[1] (%) | p-value |
|---|---|---|---|---|
| Fatal CHD plus non-fatal MI | 36% | 100 vs. 154 | 1.1% | 0.0005 |
| Total cardiovascular events and revascularization procedures | 20% | 389 vs. 483 | 1.9% | 0.0008 |
| Total coronary events | 29% | 178 vs 247 | 1.4% | 0.0006 |

1Based on difference in crude events rates occurring over a median follow-up of 3.3 years.

CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51).

In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup.

Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus nonfatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR

0.47 (0.320.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.591.17), p=0.287). The effect of atorvastatin on fatal and nonfatal cardiovascular disease was also assessed in a randomised, double-blind, multicenter, placebo controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 4075 years of age, without prior history of cardiovascular disease, and with LDLC ≤4.14 mmol/L (160mg/dl) and TG ≤6.78 mmol/L (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macro albuminuria. Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

| **Event** | **Relative Risk Reduction (%)** | **No. of Events (Atorvastatin vs Placebo)** | **Absolute Risk Reduction[1] (%)** | **p-value** |
|---|---|---|---|---|
| Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke) | 37% | 83 vs. 127 | 3.2% | 0.0010 |
| MI (fatal and non-fatal AMI, silent MI) | 42% | 38 vs 64 | 1.9% | 0.0070 |
| Strokes (Fatal and non-fatal) | 48% | 21 vs. 39 | 1.3% | 0.0163 |

1Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI =myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDLC level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 2192 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDLC was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or nonfatal stroke by 15% (HR 0.85; 95% CI, 0.721.00;p=0.05 or 0.84; 95% CI, 0.710.99;p=0.03 after adjustment for baseline factors) compared to placebo. All-cause mortality was 9.1% (216/2365) for atorvastatin versus 8.9% (211/2366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366,11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

• The risk of hemorrhagic stroke was increased in patients who entered the study with prior hemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.8419.57), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.279.82).

• The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.7114.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.571.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All-cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke. All-cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

Paediatric population

*Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 617 years old*

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDLC ≥4 mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage ≥2.

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDLC of <3.35 mmol/Lat Week 4 and if atorvastatin was well tolerated. Mean values for LDLC,TC, VLDLC, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation.

The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDLC and TC was approximately 40% and 30%, respectively, over the range of exposures.

In a second open label, single arm study, 271 male and female HeFH children 615 years of age were enrolled and treated with atorvastatin for up to three years. Inclusion in the study required confirmed HeFH and a baseline LDLC level ≥ 4 mmol/L (approximately 152 mg/dL). The study included 139 children at Tanner 1 developmental stage (generally ranging from 610 years of age). The dosage of atorvastatin (once daily) was initiated at 5 mg (chewable tablet) in children less than 10 years of age. Children age 10 and above were initiated at 10 mg atorvastatin (once daily).

All children could titrate to higher doses to achieve a target of < 3.35 mmol/L LDLC.
The mean weighted dose for children aged 6 to 9 years was 19.6 mg and the mean weighted dose for children aged 10 years and above was 23.9 mg.

The mean (+/SD) baseline LDLC value was 6.12 (1.26) mmol/L which was approximately 233 (48) mg/dL. See table 3 below for final results.

The data were consistent with no drug effect on any of the parameters of growth and development (i.e., height, weight, BMI, Tanner stage, Investigator assessment of Overall Maturation and Development) in paediatric and adolescent subjects with HeFH receiving atorvastatin treatment over the 3-year study. There was no Investigator assessed drug effect noted in height, weight, BMI by age or by gender by visit.

**TABLE 3 Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L)**

| Timepoint | N | TC (S.D.) | LDL-C (S.D.) | HDL-C (S.D.) | TG (S.D.) | Apo B (S.D.)# |
|---|---|---|---|---|---|---|
| Baseline | 271 | 7.86(1.30) | 6.12(1.26) | 1.314(0.2663) | 0.93(0.47) | 1.42(0.28)** |
| Month 30 | 206 | 4.95(0.77)* | 3.25(0.67) | 1.327(0.2796) | 0.79(0.38)* | 0.90(0.17)* |
| Month 36/ET | 240 | 5.12(0.86) | 3.45(0.81) | 1.308(0.2739) | 0.78(0.41) | 0.93(0.20)*** |

TC= total cholesterol; LDL-C = low density cholesterol-C; HDL-C = high density cholesterol-C; TG = triglycerides; Apo B = apolipoprotein B; "Month 36/ET" included final visit data for subjects who ended participation prior to the scheduled 36 month time point as well as full 36 month data for subjects competing the 36 month participation; "*"= Month 30 N for this parameter was 207; "**"= Baseline N for this parameter was 270; "***" = Month 36/ET N for this parameter was 243; "#"=g/L for Apo B.

*Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 1017 years old*

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 1017 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up titrated to 20 mg if the LDL-C level was >3.36 mmol/L. Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase. The mean achieved LDLC value was 3.38 mmol/L (range: 1.816.26mmol/L) in the atorvastatin group compared to 5.91 mmol/L (range: 3.939.96mmol/L) in the placebo group during the 26week double-blind phase.

An additional paediatric study of atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10-18 years demonstrated that atorvastatin (N=25) caused a significant reduction in LDL-C at week 26 ($p<0.05$) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-cholesterol was lowered by 36%.

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

The European Medicines Agency has waived the obligation to submit the results of studies with atorvastatin in children aged 0 to less than 6 years in the treatment of heterozygous hypercholesterolaemia and in children aged 0 to less than 18 years in the treatment of homozygous familial hypercholesterolaemia, combined (mixed) hypercholesterolaemia, primary hypercholesterolaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

Pharmacokinetic properties

**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. 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 HMGCoA 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.

Atorvastatin is ≥ 98% bound to plasma proteins. Biotransformation Atorvastatin is metabolised by cytochrome P450 3A4 to ortho and parahydroxylated derivatives and various betaoxidation products. Apart from other pathways these products are further metabolised via glucuronidation. In vitro, inhibition of HMGCoA reductase by ortho and parahydroxylated metabolites is equivalent to that of atorvastatin.

Approximately 70% of circulating inhibitory activity for HMGCoA reductase is attributed to active metabolites.

Elimination

Atorvastatin 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 HMGCoA 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.

*Paediatric population*

In an open label, 8week study, Tanner Stage 1 (N=15) and Tanner Stage ≥2 (N=24) paediatric patients (ages 617 years) with heterozygous familial hypercholesterolemia and baseline LDLC ≥4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin

tablets once daily, respectively. 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 ohydroxyatorvastatin 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. 16fold in Cmax and approx. 11fold in AUC) in patients with chronic alcoholic liver disease (Child Pugh-B).

*SLOC1B1 polymorphism*
Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter.

In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis. Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

**Fenofibrate**
Pharmacodynamic properties
Serum Lipid Reducing Agents / Cholesterol and Triglycerides Reducers / Fibrates.

ATC code: C10 AB 05

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα).

Through activation of PPARα, fenofibrate increases the lipolysis and elimination of atherogenic triglyceride rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

The above stated effects of fenofibrate on lipoproteins lead to a reduction in very low and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII.

In addition, through modulation of the synthesis and the catabolism of VLDL fractions fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease. During clinical trials with fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%. In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, all of which are markers of atherogenic risk.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all-cause mortality in the primary or secondary prevention of cardiovascular disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.791.08, p = 0.32; absolute risk reduction: 0.74%). In the prespecified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDLC (≤34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥204 mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.490.97, p = 0.03 ; absolute risk reduction: 4.95%).

Another prespecified subgroup analysis identified a statistically significant treatment by gender interaction (p = 0.01) indicating a possible treatment benefit of combination therapy in men (p=0.037) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy (p=0.069). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.
Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia. Fenofibrate has been shown to possess an antiaggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.

Pharmacokinetic properties
**Absorption:**

Maximum plasma concentrations (Cmax) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. The absorption of fenofibrate is increased when administered with food.

Distribution:
Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Metabolism and excretion:

After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified. Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibric acid is not eliminated by haemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

**PRECLINICAL SAFETY DATA**
**Atorvastatin**

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay.

Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 611 fold the $AUC_{0-24\,h}$ reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMGCoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits.

The development of the rat offspring was delayed and postnatal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

**Fenofibrate**
In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I slow Oxidative myofibres) and cardiac degeneration, anemia and decreased body weight were seen. No skeletal toxicity was noted at doses up to 30 mg/kg (approximately 17time the exposure at the human maximum recommended dose (MRHD). No sign of cardio myotoxicity were noted at an exposure about 3 times the exposure at MRHD. Reversible ulcers and erosions in the gastrointestinal tract occurred in dogs treated for 3 months. No gastrointestinal lesions were noted in that study at an exposure approximately 5 times the exposure at the MRHD.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation.

These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.
Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses.

Reversible hypospermia and testicular vacuolation and immaturity of the ovaries were observed in a repeat dose toxicity study with fenofibric acid in young dogs. However, no effects on fertility were detected in nonclinical reproductive toxicity studies conducted with fenofibrate.

**EXPIRY DATE**
Do not use later than the date of expiry.

**PACKAGING INFORMATION**
MODLIP F is available as strip of 10 tablets.

**STORAGE AND HANDLING INSTRUCTIONS**
Store at a temperature not exceeding 30ºC, protected from light and moisture.
Keep out of the reach of children.

**MARKETED BY**
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**IN/MODLIP F 10,160mg/MAY-17/02/PI**