Turkey

Divator 20 mg Film Tablet

Summary of Products Characteristics

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1. NAME OF THE MEDICINAL PRODUCT

Divator 20 mg Film Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Atorvastatin calcium equivalent to 20 mg atorvastatin

Excipients:

lactose monohydrate 41.32 mg

Crosscarmellose sodium 45.00 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film tablet

White, film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

Divator 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.

Divator is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments 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.

4.2 Posology and method of administration

Posology:

The patient should be placed on a standard cholesterol-lowering diet before receiving Divator and should continue on this diet during treatment with Divator. The dosage range is 10 mg to 80 mg once daily. The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response. Following initiation and/or titration of the treatment, lipid levels should be assessed within 2-4 weeks and the dosage should be adjusted accordingly.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

The majority of patients are controlled with Divator 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 Divator 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily if necesssary. 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 (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). 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.

Method of administration:
Divator 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.

Additional Information for Special Populations

Renal impairment:
Renal disease does not affect the plasma concentrations nor LDL-C reduction of Atorvastatin calcium tablets; thus, dosage adjustment in patients with renal dysfunction is not necessary (see section 4.4 and 5.2).

Hepatic impairment:
(see section 4.3 and 4.4).

Pediatric use (10-17 years of age) Heterozygous familial hypercholesterolaemia

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. (Doses above 20 mg and combined treatment were not studied in this patient population). The dose should be individualized to the recommended treatment goal (see section 5). Adjustments should be made at intervals of at least 4 weeks.

Use in the elderly

No differences for safety and efficacy were observed between the elderly patients and the general population at recommended doses (See section 4.4)

Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins in order to achieve additional benfits. The combination of HMG-CoA reductase inhibitors (statins) and fibrates (such as gemfibrazil, fenofibrate) should be avoided (See section 4.4 and 4.5)

Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with Atorvastatin calcium tablets should be avoided. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with Atorvastatin calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of Atorvastatin calcium is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with Atorvastatin calcium tablets should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of Atorvastatin calcium tablets is employed (See section 4.4 and 4.5).

4.3 Contraindications

Divator is contraindicated in patients:

− with hypersensitivity to the active substance or to any of the excipients of this medicinal 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

4.4 Special warnings and precautions for use

Liver effects:

Like other lipid lowering agents in same class with atorvastatin, moderate elevations in serum transaminases (3 times the upper limit of normal (ULN)) following treatment with atorvastatin have been reported. In this case reduction of dose or withdrawal of Divator is recommended. During pre-marketing and post-marketing clinical trials with 10, 20, 40 and 80 mg doses of atorvastatin, liver function was monitored.

Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received Atorvastatin calcium in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively. Increases in liver function tests (LFT) were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels. Most of the patients continued treatment with atorvastatin at a lower dose without sequelae.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with Atorvastatin calcium and repeated as clinically indicated. There have been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including Atorvastatin.

If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Atorvastatin calcium, promptly interrupt therapy. If an alternate etiology is not found, do not restart Atorvastatin calcium.

Patients treated with Divator should be warned to report promptly about any symptom that indicate liver damage including fatigue, anorexia, right upper abdominal discomfort, dark urine, and hibernation.

Atorvastatin may cause elevation in transaminase levels (See section 4.8).

Divator should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Atorvastatin in contraindicated with patients who has active liver disease or unexplained persistent transaminase elevations (see section 4.3)

Skeletal muscle effects:
Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with Atorvastatin calcium and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.
Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of Atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.
There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of

statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Atorvastatin calcium. Atorvastatin calcium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with Atorvastatin calcium and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of Atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see section 4.5). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Before the treatment for the patients with rhabdomyolysis risk:

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CPK 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 (see section 4.5) and special populations including genetic subpopulations (see section 5.2)

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.

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	**Prescribing Recommendations**
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid Atorvastatin usage
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg Atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg Atorvastatin daily

Interacting Agents	Prescribing Recommendations
*Use with caution and with the lowest dose necessary	

Cases of myopathy, including rhabdomyolysis, have been reported with Atorvastatin co-administered with colchicine, and caution should be exercised when prescribing Atorvastatin with colchicine.

In patients with severe conditions that suggest myopathy, acute or in patients with rhabdomyolysis a predisposing factor (eg, severe acute infection, hypotension, significant surgical intervention, trauma, severe metabolic, endocrine and electrolyte disturbances, and uncontrolled crises), atorvastatin treatment should be discontinued temporarily or completely.

Diabete Mellitus and Endocrin Effects:

As in other HMG-CoA reductase inhibitors, HbA1c and serum glucose levels increased in patients treated with DIVATOR. In patients with risk factors for diabetes, an increase in the incidence of diabetes was reported with Divator. However, given the benefit that HMG-CoA reductase inhibitors reduce by reducing the frequency of major cardiovascular events, the overall benefit-harm balance appears to be significantly positive, and therefore there should be no reason to discontinue statin therapy.

Risk patients (fasting blood glucose 5.6 to 6.9 mmol / L, BMI> 30 mg / m^2, increased triglycerides, hypertension) should be monitored clinically and biochemically.

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and may theoretically affect adrenal and / or gonadal steroid production. Clinical studies have shown that Atorvastatin does not reduce basal plasma cortisol concentration or does not reduce adrenal reserve. The effects of MHG-CoA reductase inhibitors on male fertility have not been studied on a sufficient number of patients. The effects, if any, on the pituitary-gonadal axis in

premenopausal women are unknown. Caution should be exercised if MHG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Hemorrhagic stroke

In a post-hoc analysis of study where atorvastain 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatşn 80 mg group compared to placebo (33 placebo against 55 atorvastatin). Patients with initially hemorrhagic stroke appear to be at greater risk for recurrent hemorrhagic stroke (2 placebo against 7 atorvastatin). Also for the patient that treated with 80 mg atorvastatin, occurrence of any type of stroke (265 patients with atorvastatin against 311 patients with placebo) and any incidence related to CHD (123 against 311) was lower. (please see section 5.1.)

Warnings for Patients

Patients should be advised to report promptly in case of unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Pediatric Use

Safety and effectiveness of atorvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration. Patients treated with atorvastatin had a safety and tolerability profile generally similar to that of placebo. The most common adverse experiences are infections regardless of causality assessment. Doses greater than 20 mg have not been studied in this patient population. In this study atorvastatin had no effect on growth or sexual maturation in boys and in girls. The effects on menstrual cycle were not assessed. Adolescent females should be counselled on appropriate contraceptive methods while on Divator therapy (See section 4.3, 4.4, 4.6). Divator has not been studied in controlled clinical trials involving pre-pubertal

patients or patients younger than 10 years of age. Information on the safety of growth and development in the pediatric population is not sufficient

Geriatric Use:
Atorvastatin plasma concentration is higher in healthy elderly population (above 65 years of age) than young adults (Cmax is approximately 40% and AUC is approximately 30%). The LDL-K reduction is similar to that seen in young patient populations receiving equal doses of atorvastatin (see section 5.2)

Interstitial lung disease:
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). 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.

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

Divator contains sodium. This should be considered for patients on a controlled sodium diet

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of cyclosporine, fibric acid derivatives (such as gemfibrozil, fenofibrate), niasin and cytochrome P450 3A4 inhibitors (such as erythromycin,

clarithromycin (see below) and azole antifungals) with HMG-CoA inhibitors may lead to increased risk of myopathy. (see section 4.4).

Atorvastatin daily dose of atorvastatin should be 10 mg in patients receiving medication that increases the plasma concentration of atorvastatin. When taking clarithromycin and itraconazole, a lower maximum atorvastatin dose should be used.

Cytochrome P450 3A4 inhibitors:
Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant administration of medicinal products that are inhibitors of P450 3A4 may lead to increased plasma concentrations of atorvastatin. The level of interaction and the increase in activity depend on the variability of the effect on cytochrome P450 3A4.

Erythromycin/clarithromycin:
The combination of atorvastatin with erythromycin (4 times a day, 500 mg) or clarithromycin (500 mg twice daily), a known inhibitor of cytochrome P450 3A4, has been associated with high plasma atorvastatin concentrations (see section 4.4). If clarithromycin should be co-administered with aortavastatin, the daily dose should not exceed 20 mg daily

Protease inhibitors
Divator's combinations of several HIV protease inhibitor combinations and the hepatitis C protease inhibitor telaprevir have significantly increased the use of atorvastatin AUC compared to the Divator alone. For this reason, patients with HIV protease inhibitor tipranavir and ritonavir or hepatitis C protease inhibitor telrevir; Divator 's use together should be avoided. Patients receiving ritonavir with the HIV protease inhibitor lopinavir should be cautious when prescribing a DIVATOR and should use the lowest dose required. In patients receiving the HIV protease inhibitor nelfinavir or hepatitis C protease inhibitor boceprevir, the DIVATOR dose should not exceed 40 m and lean clinical monitoring is recommended.

Diltiazem hydrochloride:

The concurrent use of atorvastatin (40mg) and diltiazem (240 mg) resulted in an increase in atorvastatin plasma concentrations.

Cimetidine:

Interaction with cimetidine was performed and no clinically significant interaction was observed.

Itraconazole:

Concurrent use of atorvastatin (20-40 mg) and itraconazole (200 mg) was associated with an increase in the EAA values of atorvastatin. When itraconazole is to be administered concomitantly with atorvastatin, atorvastatin should not exceed 40 mg daily.

Grapefruit Juice:

Some substances in grapefruit juice inhibit CYP3A4 and lead to elevated plasma concentrations of atorvastatin, especially if overdosed (> 1.2 liters / day)

Inducers of cytochrome P450 3A4:

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 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.

Antacids:

Co-administration of an oral antacid suspension containing magnesium and aluminum hydroxide with atorvastatin reduced plasma concentrations of atorvastatin by approximately 35%, with no change in the LDL-C reduction ratio.

Antipyrin:

Atorvastatin does not affect antipyrine pharmacokinetics. For this reason, interaction with metabolized drugs is not expected with the same cytochrome isoenzymes.

Azithromycin:

Plasma concentrations of atorvastatin did not change as a result of a single daily dose of 10 mg atorvastatin and a single dose of 500 mg azithromycin per day.

Oral contraceptives:

Administration with an oral contraceptive containing norethindrone and ethinyl estradiol caused approximately 30% and 20% increases in AUC values for norethindrone and ethinyl estradiol, respectively. When choosing oral contraceptive doses for a woman using atorvastatin, these increased concentrations should be considered.

Warfarin

When atorvastatin was given to patients receiving chronic warfarin therapy, there was no clinically significant effect on prothrombin time. However, when patients using warfarin should use DIVATOR, patients should be followed closely.

Amlodipine:

In the study of drug interactions in healthy subjects, an 18% increase in atorvastatin, which was evident in the combined use of 80 mg atorvastatin and 10 mg amlodipine, was not clinically significant.

Colchicine:

When used in combination of atorvastatin with colchicine, myopathies including rhabdomyolysis have been reported; therefore, caution should be exercised when used atorvastatin with colchicine.

Transport protein inhibitors:

Atorvastatin and its metabolites are substrates of OATP1B1 carriers. OATP1B1 inhibitors (eg cyclosporin) increase the bioavailability of atorvastatin. Concurrent use of 10 mg atorvastatin and 5.2 mg / kg / day cyclosporin resulted in a 7.7-fold increase in atorvastatin exposure.
Concomitant use of atorvastatin and cyclosporine should be avoided. (See Section 4.4, Skeletal Muscle Effects)

Gemfibozil:

Due to the increased risk of myopathy / rhabdomyolysis in combination with HMG-CoA reductase inhibitors and gemfibrozil, co-administration of Divator with gemfibrozil should be avoided.

Ezetimibe:

Ezetimibe alone is associated with muscle related events involving rhabdomyolysis. Therefore, the risk of these events may increase when atorvastatin is used in combination with ezetimibe. Appropriate clinical monitoring of these patients is recommended.

Colestipol:

When co-administered with cholestipol atorvastatin, plasma concentrations of atorvastatin were lower (approximately 25%). However, the reduction in LDL-C seen when

coadministered with atorvastatin and cholestipol was greater than when any of the medications were given alone.

Fusidic acid:

Although interaction studies with atorvastatin and fusidic acid have not been conducted, muscle problems, including rhabdomyolysis, have been reported in post-marketing experience Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Digoxin:

Coadministration of atorvastatin 10 mg and multiple doses of digoxin did not affect steady state plasma digoxin concentrations. However, following the administration of atorvastatin 80 mg daily, digoxin concentrations increased by about 20%. Patients receiving digoxin should be monitored carefully.

Other fibrates:

Care should be taken when Divator is used with other fibrates, as it is known that HMG-CoA reductase inhibitors may increase the risk of myopathy when used with other fibrates.

Niacin:

When used in combination of Divator with niacin, the risk of skeletal muscle injury may increase; in this case a reduction of the Divator dose should be considered.

Other medicines used together:

Evidence for clinically significant undesirable interactions has not been reported in clinical trials in which atorvastatin is co-administered with antihypertensive agents and estrogen replacement therapies. Interaction studies of all specific agents are not available.

4.6 Pregnancy and lactation

General Recommendation

Pregnancy category: X

Women with childbearing potential / Contraception (Contraception)

Women with childbearing potential should use appropriate contraceptive methods (see section 4.3). Atorvastatin should only be used in women of childbearing age when they are informed about potential harm that may be the fetus and only in cases where pregnancy is not possible to a great extent.

Pregnancy

Divator is contraindicated during pregnancy.

Lactation

Atorvastatin is contraindicated during breastfeeding. It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions, women taking Atorvastatin should not breast-feed their infants (see section 4.3).

Fertility

See section 5.3.

4.7 Effects on ability to drive and use machines

There are no reported adverse events that suggest that patients receiving atorvastatin will experience any deterioration in the ability to drive and use hazardous machinery.

4.8 Undesirable effects

Atorvastatin is generally well tolerated. Adverse reactions were mostly mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Divator 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 post-marketing experience, the following table presents the adverse reaction profile for Divator.

Estimated frequencies of reactions are ranked according to the following convention: very common ((≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000); rare (≥ 1/10,000, < 1/1,000); very rare (≤ 1/10,000), unknown (from available data, not known).

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, sometimes complicated by rupture.

Reproductive system and breast disorders

Uncommon: impotans
Very rare: gynecomastia.

General disorders and administration site conditions

Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, fever.

Investigations

Common: abnormal liver function tests, increased blood creatine kinase values
Uncommon: positive white blood cells in the urine

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Divator. 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% in patients took Divator. 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 Divator, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Divator - treated patients (see section 4.4).

Paediatric Population

The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Abdominal pain

Investigations

Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

The following adverse events have been reported with some statins:

• Sleep disturbance, including insomnia and nightmares.

• Loss of memory.

• Sexual dysfunction.

• Depression.

• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

• 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).

In post-marketing experience, cognitive impairment associated with statin use (eg, memory loss, forgetfulness, amnesia, memory impairment, confusion) has been reported rarely. Notifications are not usually severe, they are reversible with the discontinuation of statin use, changes in the duration of symptoms (1 day-years), and loss of symptoms (median 3 weeks).
Immune-mediated necrotizing myopathy associated with the use of statin has rarely been reported. (See Section 4.4)

4.9 Overdose and treatment

Specific treatment is not available for Divator 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 CPK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiovascular drugs, serum lipid modifying agents, HMG-CoA-reductase inhibitors,

ATC code: C10AA05

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Triglycerides and cholesterol are released into the plasma to be transported to the peripheral tissues by participating in the VLDL (very low-density lipoprotein) structure in the liver. LDL (low-density lipoprotein) is composed of VLDL and is catabolized mainly through the high-affinity LDL receptor. VLDL, IDL and cholesterol-enriched triglyceride-rich lipoproteins containing residues can increase atherosclerosis, such as LDL. Elevated plasma triglycerides are often found in a triple environment with low LDL cholesterol levels and small LDL particles, which is accompanied by non-lipid metabolic risk factors for coronary heart disease. Total plasma triglycerides alone have not been shown to be a risk factor for coronary heart disease.

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in

patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

In a total of 24 controlled trials of atorvastatin 10-80 mg, a total analysis of patients with Fredrickson type IIa and IIb hyperlipoproteinemia showed that total cholesterol, LDL-cholesterol, triglyceride levels and total-K / HDL-C and LDL-C / HDL- consistent with the results of the study. In addition, atorvastatin (10-80 mg) increased the mean dose-independent increase in HDL-C by 5.1-8.7%.

Atorvastatin and some metabolites are pharmacologically active in humans. The most important center of action for atorvastatin is the liver, the main center of cholesterol synthesis and LDL clearance. Lowering LDL-C is associated with more drug dosing than systemic drug concentration. Given the therapeutic response, the medication must be adjusted to the individual dose (see section 4.2).

Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin (atorvastatin calcium) on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels <6.5 mmol/L. Additionally all patients had at least 3 of the

following cardiovascular risk factors: male gender, age >55 years , smoking, diabetes history of CHD in a first-degree relative, TC:HDL > 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. In this double-blind, placebo-controlled study, patients were treated with antihypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.
The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	p-value
Fatal CHD plus non-fatal MI	%36	100 vs 154	0.0005
Total cardiovascular events and revascularization procedures	%20	389 vs 483	0.0008
Total coronary events	%29	178 vs 247	0.0006
Deadly and non-fatal stroke *	%26	89 vs 119	0.0332

* Although the reduction in mortal and non-fatal pulmonary arteries did not reach the pre-determined significance level (p = 0.01); with a relative risk reduction of 26%.
Risk reduction is consistent regardless of age, smoking, obesity, and renal dysfunction.

There was no significant difference between groups in terms of total mortality (p = 0.17) and cardiovascular mortality (p = 0.51).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin (atorvastatin calcium) on coronary heart disease (CHD) and non-CHD endpoints was assessed

in 2838 men and women, ages 40-75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL < 4.14 mmol/L and TG < 6.78 mmol/L. In addition to type 2 diabetes, subjects had one or more of the following CHD risk factors: current smoking, hypertension, retinopathy, microalbuminuria or macroalbuminuria. In this multicenter, placebo-controlled, double blind clinical trial of primary prevention of fatal and nonfatal cardiovascular and cerebrovascular disease in subjects with type 2 diabetes and 1 other CHD risk factor, patients were randomly allocated to either atorvastatin 10 mg daily (1429) or placebo (1411) in a 1:1 ratio.

Patients were followed for a median duration of 3.9 years. Due to significant treatment benefits ($p<0.0005$, one-sided, in favor of atorvastatin) seen early in the study, the study was stopped by the CARDS Steering Committee two years earlier than anticipated.

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37	82 vs 127	0.0010
MI (fatal and non-fatal AMI, silent MI)	42	38 vs 64	0.0070
Strokes (Fatal and non-fatal)37	48	21 vs 39	0.0163

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 LDL-C 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). The total adverse event and severe adverse event frequency in both groups were similar.

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).

In the atorvastatin group, LDL-C 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, LDL-C was reduced to a mean of 2.85 mmol/L ± 0.7 (110 mg/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 HDL-C 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.

Prevention of 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, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C 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 non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; 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 frequency of fatal hemorrhagic strokes was similar among the groups (18 placebo versus 17 atorvastatin). The reduction in the risk of cardiovascular events with atorvastatin 80 mg was seen in all patient groups except patients with recurrent hemorrhagic impairment (2 placebo vs. 7 atorvastatin) entering the study with hemorrhagic stroke.

In patients treated with atorvastatin 80 mg, there were fewer types of stroke (311 placebo versus 265 atorvastatin) and CHD events (204 placebo versus 123 atorvastatin). Total mortality rates (211 placebo vs 216 atorvastatin) were similar between the two groups. There was no difference between treatment groups in terms of total adverse event frequency.

Seconder Protection from Cardiovascular Events

In the Treating to New Targets Study (TNT), the effect of ATORVASTATIN 80 mg/day vs. ATORVASTATIN 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with ATORVASTATIN 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of ATORVASTATIN and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of ATORVASTATIN and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of ATORVASTATIN.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002. The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR* (95%CI)
PRIMARY ENDPOINT	**n**	**(%)**	**n**	**(%)**	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS†					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure‡	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint‡	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

*Atorvastatin 80 mg: atorvastatin 10 mg

†Secondary endpoints not included in primary endpoint

There was no significant difference between the treatment groups for all-cause mortality: 282 in 10 mg/day treatment group (%5.6) ; 284 in 80 mg/day treatment group (%5.7). The proportions of subjects, who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the ATORVASTATIN 80 mg group than in the ATORVASTATIN 10 mg treatment group. The proportions of subjects who

experienced noncardiovascular death were numerically larger in the ATORVASTATIN 80 mg group than in the ATORVASTATIN 10 mg treatment group.
In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study has been evaluated. This multicenter, randomized, double-blind, placebo-controlled study included 3086 acute coronary syndrome patients (with unstable angina and Q-wave myocardial infarction). They were randomized to placebo or of 80 mg groups daily atorvastatin for a mean period of 16 weeks. The final LDL-C level in the atorvastatin group was 72 mg / dL, total-K 147 mg / dL, HDL-K 48 mg / dL and tg 139 mg / dL. In the placebo group, the final LDL-C level was 135 mg / dL, total-K 217 mg / dL, HDL-K 46 mg / dL and TG 187 mg / dL. Atorvastatin significantly decreased the risk of ischemic events and death by 16%. Due to documented myocardial ischemia, the risk of relapse due to angina pectoris decreased significantly by 26%. In all of the initial LDL-K range, atorvastatin significantly reduced the risk of ischemic events and death. In addition, atorvastatin, Q-wave myocardial infarction and unstable angina, male or female, reduced the risk of ischemic event and death at similar rates in patients over 65 years of age or below.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with ATORVASTATIN 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years. An average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of ATORVASTATIN and 105, 179, 142, 47, and 132 mg/dL during treatment with 20–40 mg of simvastatin.

There was no significant difference in the ratio of the first major cardiovascular event (fatal CCD, nonfatal myocardial infarction, resuscitated cardiovascular arrest) as the primary endpoint of the study (411 (9.3%) in the ATORVASTATIN 80 mg/day group vs. 463 (10.4%) in the simvastatin 20–40 mg/day group, HR 0.89, 95% CI (0.78, 1.01), p=0.07). There were no significant differences between the treatment groups for all-cause mortality (366 (8.2%) in the ATORVASTATIN 80 mg/day group vs. 374 (8.4%) in the simvastatin 20–40 mg/day group). The proportions of subjects who experienced CV or non-CV death were similar for the ATORVASTATIN 80 mg group and the simvastatin 20–40 mg group.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal girls 10 years to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia, were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of ATORVASTATIN (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1 %).

ATORVASTATIN significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase

Lipid-altering Effects of ATORVASTATIN in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
LIPITOR	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the ATORVASTATIN group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

In this limited controlled study, girls had no detectable effect on menstrual cycle or sexual maturation and growth of boys. Atorvastatin has not been studied in controlled clinical trials in pre-puberty patients or in children under 10 years of age. The safety and efficacy of doses above 20 mg have not been tested in controlled studies in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality during adulthood has not been determined.

5.2 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 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether ATORVASTATIN is given with or without food. Plasma ATORVASTATIN concentrations are lower (approximately 30% for

Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see section 4.2)

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins. Erythrocyte/plasma ratio of approximately 0.25 indicates poor penetration of drug into red blood cells.

Biotransformation

ATORVASTATIN is substantially metabolized with cytochrome P450 3A4 to ortho- and para hydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of ATORVASTATIN. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of ATORVASTATIN metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of ATORVASTATIN in humans following co-administration with erythromycin, a known inhibitor of this isozyme. Ayrıca in vitro çalışmalar göstermektedir ki atorvastatin sitokrom P4503A4'ün zayıf bir inhibitörüdür. Co-administration of athervastatin with terfenadine, a compound largely metabolized by cytochrome P4503A4, does not significantly affect plasma concentrations of terfenadine as clinically significant. Therefore, atorvastatin is not expected to significantly alter the pharmacokinetics of other cytochrome P4503A4 substrates (see Section 4.5). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

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

Special populations

Geriatric:

Plasma concentrations of ATORVASTATIN are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. The ACCESS study assessed elderly patients in particular in terms of achieving NCEP treatment goals. There were 1087 under 65, 815 over 65, and 185 over 75 years of age. There was no difference between elderly patients and the entire population in terms of achieving safety, efficacy, or lipid treatment goals.

Pediatric:

Pharmacokinetic data in the pediatric population are not available.

Gender:

Plasma concentrations of ATORVASTATIN in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in lipid reduction with ATORVASTATIN between men and women.

Renal Impairment:

Renal disease has no influence on the plasma concentrations or LDL-C reduction of ATORVASTATIN; thus, dose adjustment in patients with renal dysfunction is not necessary (see section 4.2).

Hemodialysis:

While studies have not been conducted in patients with end-stage renal disease. Hemodialysis is not expected to significantly enhance clearance because of the drug is extensively bound to plasma proteins.

Hepatic Impairment:

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are significantly increased (approximately 16 times Cmax, 11 times) (Childs-Pugh B disease) (see section 4.3).

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 (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

Drug Interactions

The effects of coadministration of atorvastatin on the pharmacokinetics of atorvastatin and the pharmacokinetics of atorvastatin coadministered drugs are given in the following table **(see**

section 4.4 Special warnings and precautions for use, and section 4.5 Interactions with other medicinal products and other forms of interaction).

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC&	Change in C_{max}&
#Cyclosporine 5.2 mg/kg/day, stable dose	Once a day 10 mg per day for 28 days	↑ 8.7 fold	↑10.7 fold
#Tipranavir 500 mg, twice a day /ritonavir 200 mg, twice a day,7 days	Single dose 10 mg	↑ 9.4 fold	↑ 8.6 fold
#Telaprevir 750 mg q&h, 10 days	Single dose 20 mg	↑ 7.88 fold	↑ 10.6 fold
#Saquinavir 400 mg, twice a day /ritonavir 400 mg, twice a day,15 days	40 mg once a day for 4 days	↑ 3.9 fold	↑ 4.3 fold
#Clarithromycin 500 mg , twice a day, 9 days	80 mg once a day for 8 days	↑ 4.4 fold	↑ 5.4 fold
#Darunavir 300 mg, twice a day /ritonavir 100 mg, twice a day, 9 days	10 mg once a day for 4 days	↑ 3.4 fold	↑ 2.25 fold
#Itraconazole 200 mg, once a day, 4 days	Single dose 40 mg	↑ 3.3 fold	↑ 20%
#Fosamprenavir 700 mg, twice a day /ritonavir 100 mg twice a day, 14 days	10 mg once a day for 4 days	↑ 2.53 fold	↑ 2.84 fold
#Fosamprenavir 1400 mg , twice a day, 14 days	10 mg once a day for 4 days	↑ 2.3 fold	↑ 4.04 fold
#Nelfinavir 1250 mg ,twice a day, 14 days	10 mg once a day for 28 days	↑ 74%	↑ 2.2 fold
#Grapefruit Juice, 240 mL , once a day*	Single dose 40 mg	↑ 37%	↑ 16%
Diltiazem 240 mg, once a day, 28 days	Single dose 40 mg	↑ 51%	No change
Erythromycin 500 mg, four times a day, 7 days	Single dose 10 mg	↑ 33%	↑ 38%

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	**Change in AUC&**	**Change in Cmax&**
Amlodipine 10 mg, single dose	Single dose 80 mg	↑ 15%	↓ 12 %
Cimetidine 300 mg, once a day, 4 weeks	10 mg once a day for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg, twice a day, 28 weeks	for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 ml, once a day, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg, once a day, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
#Rifampin 600 mg, once a day, 7 days (co-administered) †	Single dose 40 mg	↑ 30%	↑ 2.7 fold
#Rifampin 600 mg , once a day, 5 days (in separate doses) †	Single dose 40 mg	↓ 80%	↓ 40%
#Gemfibrozil 600 mg , twice a day, 7 days	Single dose 40mg	↑ 35%	↓ Less than 1%
#Fenofibrate 160 mg , once a day, 7 days	Single dose 40mg	↑ 3%	↑ 2%
Boceprevir 800 mg , three times a day, 7 days	Single dose 40 mg	↑2.30	↑2.66 fold

& ‘ fold’ change = rate change [(I-B)/B], I= pharmacokinetic value during the interaction phase,

B= pharmacokinetic value during baseline phase,% change=% rate change

See Sections 4.4 and 4.5 for clinical significance.

* The area under the curve (AUC) (up to 1.5 fold) and / or Cmaks (up to 71%) have also been reported to be large increases with excessive grapefruit consumption(≥ 750 mL - 1.2 liters per day).

** Single sample taken 8 to 16 h post dose.

†Due to the dual interaction mechanism of rifampin, 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 dose of saquinavir and ritonavir dose in this study is not the clinically used dose. The increase in Atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC[&]	Change in Cmax[&]
80 mg once a day for 15 days	Antipyrine, single dose 600 mg	↑ 3% fold	↓ 0.11% fold
80 mg once a day for 14 days	[#]Digoxin 0.25 mg, once a day, 20 days	↑ 15% fold	↑ 20 % fold
40 mg once a day for 22 days	Oral contraceptive once a day, 2 months - norethindrone 1mg - ethinyl estradiol 35 µg	 ↑ 28% fold ↑ 19% fold	 ↑ 23% fold ↑ 30% fold
Single dose 10	Tipranavir 500 mg	No change	No change

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC[&]	Change in Cmax[&]
mg	twice a day /ritonavir 200 mg twice a day, 7 days		
10 mg once a day for 4 days	Fosamprenavir 1400 mg, twice a day, 14 days	↓ 27%	↓ 18%
10 mg once a day for 4 days	Fosamprenavir 700 mg twice a day/ritonavir 100 mg twice a day, 14 days	No change	No change

& 'fold' change = rate change [(I-B)/B], I= pharmacokinetic value during the interaction phase,

B= pharmacokinetic value during baseline phase,

See Section 4.5 for clinical significance.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Atorvastatin was not found to be carcinogenic in rats. The maximum dose used was 63 times higher in mg / kg body weight than the highest human dose (80 mg / day) and 8-16 times higher on the EAA (0-24) value. In a two-year study in mice; the incidence of hepatocellular adenoma in males and hepatocellular carcinoma in females, the maximum dose used; mg / kg body weight, 250 times more than the highest human dose. Systemic utilization was 6-11 times higher when based on EAA (0-24). All chemically similar drugs in this class induced tumors in both mice and rats at 12 to 125 fold of the highest recommended clinical dose in mg / body weight in weight.

Demonstrate atorvastatin, mutagenic, or clastogenic potential in in vitro tests with metabolic

activation and inactivation (in AMES test with Salmonella typhimurium and Escherichia coli, in vitro HGPRT forward mutation test in Chinese hamster lung cells, chromosomal aberration test with Chinese hamster lung cells). Also atorvastatin is negative in *in vivo* mouse micronucleus test.

In animal studies, no animal adverse effects on fertility were observed at doses of 175-225 mg / kg / day in male and female rats of atorvastatin. These doses are 100 to 140 times the recommended maximum human dose on a mg / kg body weight basis. Atorvastatin at 10, 40 or 120 mg / kg doses given for two years did not cause any adverse effects in dogs, sperm or semen parameters or in the histopathology of the reproductive organs.

There is evidence from experimental animal studies that HMG-CoA reductase inhibitors may affect embryo and fetal development. In rats, rabbits and dogs, atorvastatin has no effect on fertility and is not teratogenic. However, maternally toxic doses of fetal toxicity were observed in rats and rabbits. During mothers' exposure to atorvastatin in high doses; the development of rat pups is delayed and postnatal survival is reduced. In rats; There is evidence of placental transfusions. In rats, plasma concentrations of atorvastatin are milk-like. It is not known whether atorvastatin or its metabolites are excreted in human beings' milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Carbonate
Lactose Monohydrate
Microcrystalline Cellulose
Croscarmelose Sodium
Hydroxy propyl cellulose
Polysorbate 80

Magnesium Stearate

Purified water

Film-coating (Polyvinyl alcohol, Titanium dioxide, PEG 3350 Powder, Talk)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

PVC/ Alu / PA – aluminum blisters

Packagings with 30 film coated tablets and 90 film coated tablets.

6.6 Special precautions for disposal and other handling

Any unused products or waste materials must be disposed of in accordance with 'The Medical Waste Control Regulations' and 'The Packaging and Packaging Waste Control Regulations'.

7. MARKETING AUTHORISATION HOLDER

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