Torvalipin
Atorvastatin

1. NAME OF THE MEDICINAL PRODUCT
Torvalipin tablets 10 mg
Torvalipin tablets 20 mg
Torvalipin tablets 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 10mg of Torvalipin film-coated tablet contains atorvastatin calcium corresponding to 10mg of atorvastatin base.
Each 20mg of Torvalipin film-coated tablet contains atorvastatin calcium corresponding to 20mg of atorvastatin base.
Each 40mg of Torvalipin film-coated tablet contains atorvastatin calcium corresponding to 40mg of atorvastatin base.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
10 mg: White, oval, biconvex film-coated tablets marked with "10" on one side and "A" on the other".
20 mg: White, oval, biconvex film-coated tablets marked with "20" on one side and "A" on the other".
40 mg: White, oval, biconvex film-coated tablets marked with "40" on one side and "A" on the other".

4. Clinical particulars
4.1 Therapeutic indications
Hypercholesterolaemia
Torvalipin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDLcholesterol, apolipoprotein B, or triglycerides in patients with primary hypercholesterolaemia including heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia (such as Frederickson's types IIa and IIb), when satisfactory results have not been obtained by a special diet or measures other than medication.
Torvalipin is also indicated to reduce totalcholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Prevention of Cardiovascular Disease
Torvalipin is indicated to reduce the risk of myocardial infarction in adult hypertensive patients without clinically evident coronary heart disease, but with at least three additional risk factors for coronary heart disease such as age ≥ 55 years, male sex, smoking, left ventricular hypertrophy, other specified abnormalities on ECG, microalbuminia or proteinuria, ratio of plasma total cholesterol to HDL-cholestrol ≥ 6, or premature family history of coronary heart disease.

In patients with type 2 diabetes and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking or hypertension, Torvalipin is indicated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin is indicated to:
- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk of revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

4.2 Posology and method of administration
For oral administration.
The patient should be placed on a standard cholesterol-lowering diet before receiving Torvalipin and should continue on this diet during treatment with Torvalipin. Doses should be determined individually according to the baseline LDL-cholesterol value, treatment objective and patient response.
The usual starting dose is 10 mg once a day. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.
The daily dose should be administered all at once and can be taken at any time of the day, with or without food.
Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir
Current consensus guidelines should be consulted to establish treatment goals for individual patients.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
An appropriate dose for most patients is 10 mg Torvalipin a day. A response is evident within 2 weeks and maximum response is usually achieved within 4 weeks. The response is maintained during long term treatment.

Heterozygous familial hypercholesterolaemia
Initial dose is 10 mg Torvalipin a day. Doses should be determined for each patient and adjusted at 4 week intervals up to 40 mg a day. Then the dose can be increased to either a maximum of 80 mg a day or administer 40 mg of atorvastatin once a day in combination with a bile acid sequestrant.
Homozygous familial hypercholesterolaemia
In a compassionate-use study of patients with homozygous familial Hypercholesterolaemia, most patients respondedto 80 mg of atorvastatin with a greater than 15% reduction in LDL-C (18% - 45%).

Prevention of cardiovascular disease
In the primary prevention trials the dose was 10 mg/day. Higher dosages may be necessary in order to attain LDL-cholesterol levels according to current guidelines.

Patients with impaired renal function
Renal diseases neither affect plasma concentration nor the effects of atorvastatin on blood lipids and therefore no dose adjustment is required.
Patients with impaired liver function
Torvalipin should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Torvalipin is contraindicated in patients with active liver disease (see section 4.3).

Elderly
Efficacy and safety of the use of recommended doses for patients over 70 years old are similar as for other adults.

Paediatric use
Experience in paediatric population is limited to a small number of patients with homozygous familial hypercholesterolemia (see section 5.1). Developmental safety data in this population have not been evaluated.

4.3 Contraindications
Torvalipin is contraindicated in:
- Patients with a history of hypersensitivity to the active substance or to any of the excipients.
- Patients with an active liver disease or unexplained persistent elevation of serum transaminase levels where the elevation is exceeding three times the mean upper limits.
- Patients with myopathy.
- Pregnant and breast feeding women and women of child bearing potential not using contraceptives (see section 4.6).
- Patients who are concomitantly treated with glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use
Liver effects
It is recommended that liver function tests be performed before the initiation of treatment, at 12 weeks after initiation of therapy or elevation of dose and periodically (e.g. six months) thereafter. Liver function tests should be performed if signs or symptoms of possible liver damage are observed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. In case of an elevation of transaminase levels exceeding three times the mean upper limit, dose reduction is recommended or discontinuation of treatment with Torvalipin (see section 4.8).
Torvalipin should be used with caution in patients who consume substantial amounts of alcohol and/or have a history of liver disease.

Previous stroke
A post-hoc analysis of subtypes of stroke in patients without coronary heart disease, who newly had a stroke or TIA, demonstrated higher incidence of hemorrhagic stroke in patients treated with 80 mg atorvastatin compared with placebo. The increased risk was seen especially in patients with a history of hemorrhagic stroke or lacunar infarct at the start of the trial. Benefit/risk ratio for atorvastatin 80 mg has not been established for patients with history of hemorrhagic stroke and lacunar infarct. The potential risk of hemorrhagic stroke should be carefully considered before the start of the treatment (see section 5.1)

Skeletal muscle effects
Atorvastatin, as other HMG-CoA reductase inhibitors can rarely influence skeletal muscles and cause myalgia, myositis and myopathy which can devolve into rhabdomyolysis, which is a potentially fatal condition and is characterized by an elevated CPK value (exceeding ten times ULN), myoglobinaemia and myoglobinuria, which can cause renal failure.

Prior to treatment initiation
Atorvastatin should be used with caution in patients predisposed for rhabdomyolysis. Creatine phosphokinase (CPK) levels should be measured prior to initiating treatment with statins in case of:
- Renal impairment.
- Hypothyroidism.
- Personal or familial history of hereditary muscular disorders.
- Previous history of muscular toxicity with a statin or fibrate.
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed.
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In these situations, the risk of treatment should be considered carefully with respect to the possible benefits and clinical monitoring is recommended. If the CPK values are significantly elevated, exceeding five times ULN, treatment shall not be started.

Creatine phosphokinase (CPK) measurements
CPK should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase, since that makes interpretation difficult. If the CPK value is significantly high (five times ULN), the measurement should be repeated after 5 - 7 days for confirmation.

During treatment
- The importance of immediate reporting of myalgia, cramps or fatigue, especially followed by malaise and fever, must be explained to the patients.
- If these symptoms emerge during treatment with atorvastatin CPK values should be measured and in case of elevation exceeding five times ULN, treatment should be discontinued.
- If symptoms from muscles are severe or cause daily discomfort, discontinuation of treatment should be considered, even though CPK values are not over five times ULN.
- If symptoms resolve and CPK values become normal, treatment with atorvastatin or another statin can be considered, at the lowest dose and close monitoring.
- If significant elevation of CPK values (exceeding ten times ULN) or rhabdomyolysis emerge or is suspected, treatment with atorvastatin should be discontinued.

The risk of rhabdomyolysis is increased by concurrent use of atorvastatin and certain other medicinal products which can increase atorvastatin plasma concentration such as ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozile, other fibrates and HIVprotease inhibitors. The risk of myopathy can also be increased during concurrent administration of atorvastatin and ezetimibe. Different treatment (that does not interact) should be considered, if possible. When concomitant treatment of these substances and atorvastatin is necessary, the benefit and the risk of the treatment should be carefully considered. A lower starting dose of atorvastatin is recommended for patients during concomitant use of products that increase atorvastatin plasma concentration, during concurrent use of ciclosporin, clarithromycin or itraconazol, a lower maximal dose of atorvastatin is recommended and these patients should be clinically monitored as appropriate (see section 4.5).

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.
The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated. Long term effects on cognitive development, growth and pubertal maturation are unknown.

4.5 Interaction with other medicinal products and other forms of interaction
The risk of myopathy during use of HMG-CoA reductase inhibitors is increased by concurrent use of ciclosporin, fibrates, macrolide antibiotics, including erythromycin, azole antifungals, HIVprotease inhibitors or niacin and has rarely led to rhabdomyolysis and renal insufficiency caused by myoglobinuria. Therefore, possible benefits and the risk involved with concurrent treatment must be considered carefully. When concomitant administration of these substances and atorvastatin is necessary, the benefit and the risk of the treatment should be considered carefully. A lower starting dose of atorvastatin is recommended for patients during concomitant use of products that increase atorvastatin plasma concentration. During administration of ciclosporin, clarithromycin or itraconazole, a lower maximal dose of atorvastatin is recommended and these patients should be monitored clinically as appropriate (see section 4.4).

Cytochrome P450 3A4 inhibitor
Atorvastatin is metabolised by cytochrome P450 3A4. Interactions can occur during concurrent administration of atorvastatin and a cytochrome P450 3A4 inhibitor (e.g. ciclosporin, macrolide antibiotics, including erythromycin and clarithromycin, nefazodone, azole antifungals, including itraconazole and HIV protease inhibitors). Special precaution is therefore required during concurrent administration of atorvastatin and these products because it can result in elevated plasma concentration of atorvastatin (see also section 4.4).

Transport protein inhibitors
Atorvastatin and its metabolites are substrates of OATP1B1 transporters. Concomitant use of 10 mg atorvastatin and 5.2 mg/kg/day of ciclosporin resulted in 8.7-fold increasing in atorvastatin exposure. When concurrent administration of atorvastatin and ciclosporin is necessary, the atorvastatin dose should not be higher than 10 mg.

Erythromycin, clarithromycin
Erythromycin and clarithromycin are known inhibitors of the enzyme system cytochrome P450 3A4. Concurrent administration of 80 mg atorvastatin once a day and erythromycin (500 mg four times a day) resulted in 33% increase in exposure of atorvastatin total activity. Concurrent administration of 10 mg atorvastatin daily and clarithromycin (500 mg twice a day) resulted in 4.4-fold increase in exposure of atorvastatin. When concurrent administration of atorvastatin and clarithromycin is necessary, lower maintainance doses are recommended for atorvastatin. At doses higher than 40 mg, suitable clinical monitoring of the patients is recommended.

Itraconazole
Concurrent administration of atorvastatin 20 to 40 mg and itraconazole 200 mg a day resulted in 2.5-3.3-fold increase in exposure of atorvastatin. When concurrent administration of itraconazol and atorvastatin is necessary, lower maintainance doses are recommended for atorvastatin. At doses higher than 40 mg, suitable clinical monitoring of the patients is recommended.

Protease inhibitors
Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC (see **section 4.2 Posology and method of administration - Use in Combination with Other Medicinal Compounds**)

Diltiazem hydrochloride
Concurrent administration of 40 mg atorvastatin and 240 mg diltiazem resulted in 51% increase in exposure of atorvastatin. Appropriate clinical monitoring is recommended for these patients after initiation of diltiazem and after dose adjustments.

Ezetimib
The use of ezetimib as monotherapy is associated with myopathy. The risk of myopathy can therefore be increased with concurrent administration of ezetimib and atorvastatin.

Grape fruit juice
Grape fruit juice contains one or more CYP3A4 inhibitors and can cause elevation in plasma concentration of medicinal products metabolised by CYP3A4. AUC for atorvastatin increased by 37% and AUC of the active orthohydroxy metabolite decreased by 20.4% following intake of 1 glass (240 ml) of grape fruit juice. A large amount of grape fruit juice (exceeding 1.2 l a day for five days) however causes a 2.5-fold increase in the AUC for atorvastatin and a 1.3-fold increase in AUC for the active substances (atorvastatin and metabolites) (confirm the figure). Drinking large amounts of grape fruit juice is therefore not recommended during atorvastatin treatment.

Cytochrome P450 3A4 inducers
Concurrent administration of atorvastatin and cytochrome P450 3A4 inducers (e.g. efavirenz, rifampin, phenytoin or St. John's Worth) can result in variable reductions of plasma concentration of atorvastatin. Due to the double interaction mechanism of rifampin (cytochrome P450 3A4 induction and blocking of the transport protein OATP1B1 in the hepatocytes), it is recommended to administer atorvastatin and rifampin at the same time since the administration of atorvastatin after administration of rifampin has been connected with significant reduction of plasma concentration of atorvastatin.

Verapamil and amiodarone
Interaction studies of atorvastatin and verapamil and aminodarone have not been done. It is evident that both verapamil and amiodarone inhibit the CYP3A4 activity and concurrent administration of atorvastatin can result in increased exposure of atorvastatin.

Concurrent use of other medicinal products
Gemfibrozil/fibrates
The administration of fibrates as monotherapy is associated with myopathy. Risk of atorvastatin induced myopathy can be increased during concurrent administration of fibrates (see section 4.4). Concomitant administration of 600 mg gemfibrozil twice daily resulted in 35% increase in the exposure of atorvastatin.

Digoxin
Repeated administration of digoxin and atorvastatin 10 mg at the same time did not influence the steady state plasma concentration of digoxin. Digoxin concentration however increased by ca. 20% during concurrent use of digoxin and atorvastatin 80 mg a day. Patients treated with digoxin should be monitored carefully.

Oral contraceptives
Co-administration with an oral contraceptive containing norethindrone and ethinyl estradiol increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptives for a woman taking atorvastatin.

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

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

Warfarin
An atorvastatin interaction study with warfarin was conducted, and no clinically significant interactions were seen.

Cimetidine
In the one study available of interactions between cimetidine and atorvastatin no interaction was seen.

Amlodipine
An interaction study on healthy voluntary subjects showed that concomitant administration of atorvastatin 80 mg and amlodipine 10 mg resulted in 18% increase in the exposure of atorvastatin.

Other interactions
In clinical studies no clinically significant interactions were observed when atorvastatin was administered together with antihypertensives or hypoglycemic agents.
Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin and concomitant use with atorvastatin is contraindicated.

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary. Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir.

4.6 Pregnancy and lactation
Torvalipin is contraindicated in pregnancy. Women of child bearing potential should use adequate contraceptive measures. Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.
Atorvastatin is contraindicated while breast-feeding. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed.

4.7 Effects on ability to drive and use machines
Atorvastatin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued form clinical trials due to the side effects attributed to atorvastatin.
The most frequent (≥1%) adverse effects associated with atorvastatin therapy, in patients participating in controlled clinical studies were:

Psychiatric disorders:
Insomnia.

Nervous system disorders:
Headache.

Gastrointestinal disorders:
Nausea, diarrhea, abdominal pain, dyspepsia, constipation, flatulence.

Musculoskeletal and connective tissue disorders:
Myalgia.

General disorders and administration site conditions:
Asthenia.

AAAM3620 - Atorvastatin Calcium Crystalline All strengths -, PIL (blister packaging), Singapore

GENERAL INFORMATION			
Proof Round:	6	**Dimensions:**	190x500 mm
Origination Date:	19/08/2020	**Manuf. site:**	Actavis MT Zejtun
Originated by:	v.b.m	**Min pt size:**	8 pt
Revision Date:	12/11/2020	**SAP Code:**	
Revised by:	IG		

TECHNICAL CHECK	
Date Sent:	19/08/2020
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teva
awstudio@tevapharm.com

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The following additional adverse effects have been reported in atorvastatin clinical trials:
Metabolism and nutrition disorders:
Hypoglycemia, hyperclycemia, anorexia.

Nervous system disorders:
Peripheral neuropathy, paresthesia.

Gastrointestinal disorders:
Pancreatitis, vomiting.

Hepatobilliary disorders:
Hepatitis, cholestatic jaundice.

Skin and subcutaneous tissue disorders:
Alopecia, pruritus, rash.

Muscuskeletal and connective tissue disorders:
Myopathy, myositis, muscle cramps.

Reproductive system and breast disorders:
Impotence.
Not all effects listed above have been causally associated with atorvastatin therapy.

In post marketing experience, the following additional undesirable effects have been reported: **Blood and lymphatic system disorders**: thrombocytopenia, **Immune system disorders**: allergic reactions (including anaphylaxis), **Injury, poisoning and procedural complications**: tendon rupture, **Metabolism and nutrition disorders**: weight gain, **Nervous system disorders**: hypoesthesia, amnesia, dizziness, dysgeusia, **Ear and labyrinth disorders**: tinnitus, **Skin and subcutaneous tissue disorders**: Steven-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, bullous rashes, urticaria, **Muscoskeletal and connective tissue disorders**: rhabdomolysis, arthralgia, back pain, **General disorders and Administration site conditions**: chest pain, peripheral edema, malaise, fatigue.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Increases in HbA1c and fasting serum glucose levels have been reported with statins.

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C 10 A A 05
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the ratelimiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzymeA to mevalonate, a precursor of sterols, including cholesterol.
Triglycerides and cholesterol in the liver are incorporated into VLDL (very low density lipoproteins) and released into the blood for delivery to peripheral tissues. Lowdensity lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.
Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver. Atorvastatin also increases the number of hepatic LDL receptors on the cell surface in the liver, which results in 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 reduces LDL-cholesterol significantly in patients with homozygous familial hypercholesterolaemia, but that group of patients has usually not responded to blood lipid reducing treatment.
Atorvastatin has been shown to reduce total cholesterol (30-46%), LDL-cholesterol (41-61%), apolipoprotein B (34-50%) and triglycerides (14-33%), but to cause variable increases in HDL cholesterol and apolipoprotein A1 in a dose response studies.

Atherosclerosis
In the REVERSAL (Reversing Atherosclerosis with Aggressive Lipid-Lowering Study), the effect of aggressive lipid lowering with atorvastatin 80 mg and lipid lowering to standard levels with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease.
In this randomized, 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 atovastatin were statistically significant (p=0.02). The effect of intensive lipid reduction on cardiovalsculare endpoints (e.g. the need for revascularisation, nonfatal myocardial infarction, coronary death) was not investigated in this study.
In the atorvastatin group, LDL-cholesterol was reduced to a mean value of 2.04 mmol/l ± 0.8 (78.9 mg/dl ± 30) from baseline value 3.89 mmol/l ± 0.7.
In the pravastatin group , LDL-cholesterol was reduced to a mean value of 2.85 mmol/l ± 0.7 (110 mg/dl ± 26) from baseline value 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 HDLcholesterol by 2.9% (pravastatin: +5.6%, p=NS).
There was a 36.4% mean reduction in creactive protein (CRP) in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).
The study results were obtained with 80 mg doses of atorvastatin and can therefore not be extrapolated to lower doses.
The safety and tolerability profiles of the two treatment groups were comparable.
The effect of intensive lipid lowering with atorvastatin on cardiovascular mortality and morbidity 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.

Heterozygous familial hypercholesterolaemia in paediatric patients
In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 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. Inclusion in the study required 1) a baseline LDL-cholesterol level ≥4.91 mmol/l or 2) a baseline LDL-cholesterol ≥4.14 mmol/l and positive family history of FH or documented premature cardiovascular disease in a first- or second degree relative. The mean baseline LDL-cholesterol value was 5.65 mmol/l (range: 3.58-9.96 mmol/l) in the atorvastatin group compared to 5.95 mmol/l (range: 4.14-8.39 mmol/l) in placebo group. The dosage f atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg of the LDL-cholesterol level was >3.36 mmol/l. The number of Atorvastatin-treated patients who required up-titration to 20 mg after week 4 during the double-blind phase was 80 (57.1%).
Atorvastatin significantly decreased plasma levels of total-cholesterol, LDL-cholesterol, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see table 1).

TABLE 1. Lipid altering effects of atorvastatin in adolescent boys and girls with heterozygous familial hypercholesterolaemia or severe hypocholesterolaemia (mean percent change from baseline at endpoint in intention- to-treat-population.

Atorvastatin Dose (mg)	N	Total-C (%)	LDL-C (%)	Apo B (%)	TG (%)	HDL-C (%)
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-cholesterol value was 3.38 mmol/l (range: 1.816.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.939.96 mmol/l) in the placebo group during the 26-week double-blind phase.
In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual length in girls. Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and nonfatal coronary heart disease was assessed in a randomized, doubleblind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 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=5168) or placebo (n=5137).
The absolute and relative risk reduction effect of atorvastatin was as follows:

Events Relative Risk	Reduction (%)	No. of Events (atorvastatin vs placebo)	Absolute Risk Reduction[1] (%)	pvalue
Major cardiovascular events (fatal and nonfatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	36%	100 vs 154	1.1%	0.0005
MI (fatal and nonfatal, AMI, silent MI)	20%	389 vs. 483	1.9%	0.0008
Strokes (fatal and nonfatal)	29%	178 vs. 247	1.4%	0.0006

[1]Based 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. Total mortality 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 and 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 randomized, doubleblind, multicenter, placebocontrolled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-cholesterol ≤4.14 mmol/l (160 mg/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 macroalbuminuria.
Patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median followup of 3.9 years.
The absolute and relative risk reduction effect of atorvastatin was as follows:

Events Relative Risk	Reduction (%)	No. of Events (atorvastatin vs placebo)	Absolute Risk Reduction[1] (%)	pvalue
Major cardiovascular events (fatal and nonfatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	37%	83 vs 127	3.2%	0.0010
MI (fatal and nonfatal, AMI, silent MI)	42%	38 vs. 64	1.9%	0.0070
Strokes (fatal and nonfatal)	48%	21 vs. 39	1.3%	0.0163

[1]Based 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 LDL-cholesterol 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).

Previous stroke
In the study "Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)", the effect of atorvastatin 80 mg daily on stroke in 4731 patients with no known coronary heart disease (CHD) who have had a stroke or an ischemic attack (TIA) within the last 6 months was evaluated and compared with placebo. Of the patient group 60% were males, 21-92 years old (mean 63 years) with a mean LDL-cholesterol level 3.4 mmol/l (133 mg/dl) at the initiation of the treatment. The mean LDL-cholesterol level was 1.9 mmol/l (73 mg/dl) for the atorvastatin group and 3.3 mmol/l (129 mg/dl) for the placebo group. The median of followup was 4.9 years.

A reduction seen for atorvastatin 80 mg in the primary endpoint for fatal or nonfatal stroke was 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 baseline factors) compared to placebo. Total mortality (all causes) was 9.1% (216/2365) for atorvastatin compared to 8.9% (211/2366) for placebo.
A post-hoc analysis for atorvastatin 80 mg showed a reduced incidence of ischemic stroke (218/2365, 9.2% versus 274/2366, 11,6%, p=0.01) and increased incidence of haemorrhagic stroke (55/2365, 2,3% versus 33/2366, 1,4%, p=0.02) compared to placebo.
- The risk of haemorrhagic stroke was increased in patients with a history of haemorrhagic stroke when joining the study (7/45 for atorvastatin compared with 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk for ischemic stroke was similar for both groups (3/45 for atorvastatin compared with 2/48 for placebo; HR 1.64; 95% CI, 0.279.82).
- The risk of haemorrhagic stroke was increased in patients who joined the study with a history of an lacunar infarct (20/708 for atorvastatin compared to 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61) but the risk for ischemic stroke reduced also in these patients (79/708 for atorvastatin compared to 102/701 for placebo; HR 0.76; 95% CI; 0.571.02). It is possible that the net risk for a stroke is increased in patient with a history of lacunar infarct taking atorvastatin 80 mg daily.

The total mortality (all causes) was 15.6% (7/45) for atorvastatin compared to 10.4% (5/48) for the placebo group for patients with a history of a hemorrhagic stroke. The total mortality was 10.9% (77/708) for atorvastatin compared to 9.1% (64/701) for placebo in a subgroup of patients with a history of lacunar infarct.

5.2 Pharmacokinetic properties
Absorption
Atorvastatin is rapidly absorbed following oral administration; maximum plasma concentration (C_{max}) is obtained within 1-2 hours. Extent of absorption increases in proportion to the atorvastatin dose.
Bioavailability of atorvastatin following intake of filmcoated tablets is 95-99% compared to the bioavailability of atorvastatin solutions. Absolute bioavailability is about 12% and systemic availability of the active HMG-CoA reductase inhibitor is about 30%. The low systemic availability is due 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.

Metabolism
Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various betaoxidation products. Apart from other pathways these compounds are further metabolized by glucuronisation. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion
Atorvastatin is excreted primarily in bile following hepatic and/or extrahepatic metabolism. Atorvastatin does however not appear to undergo significant enterohepatic recirculation. Mean plasma metabolism half-life of atorvastatin in humans is approximately 14 hours. Due to the active metabolites the halflife of inhibitory activity for HMG-CoA reductase is approximately 20-30 hours.

Special patient groups
- Elderly: Concentrations of atorvastatin and its active metabolites in plasma are higher in healthy elderly individuals than in those who is younger, but the blood lipid effects are similar in both age groups.
- Children: Pharmacokinetic data for children is not available.
- Gender: Concentrations of atorvastatin and its active metabolites differ in women (maximum plasma concentration is about 20% higher and AUC about 10% lower) from those in men. This difference is not of clinical relevance, and the difference in effects on blood lipids between men and women is not significant.
- Renal impairment: Renal diseases neither affect plasma concentration nor blood lipid effects of atorvastatin and its active metabolites.
- Hepatic impairment: Plasma concentration of atorvastatin and its active metabolites increases significantly (C_{max} approximately 16-fold and AUC 11-fold) in patients with chronic alcoholic liver disease (Childs-Pugh B).

Co-administered drug and dosing regimen	*Atorvastatin*		
	Dose (mg)	*Change in AUC*	*Change in C_{max}*
Glecaprevir 400 mg QD/Pibrentasvir 120 mg QD, 7 days	*10 mg QD for 7 days*	*↑ 8.3 fold*	*↑ 22.0 fold*
Elbasvir 50 mg QD/ grazoprevir 200 mg QD, 13 days	*10 mg single dose*	*↑ 1.95 fold*	*↑ 4.3 fold*

5.3 Preclinical safety data
Atorvastatin was not carcinogenic in rats. The maximum dose used was 63 times higher than the highest human dose (80 mg/day) on a mg/kg body weight basis and 8 to 16 times higher based on AUC (0-24) values as determined by total inhibitory activity.
In a 2 year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum doses used, which were 250 times higher than the highest human dose used on a mg/kg body weight basis. The systemic exposure to the mice was 6 to 11 times greater based on AUC (0-24).
Atorvastatin neither demonstrated mutagenic nor clastogenic potential in four in vitro studies with or without metabolic activation and one in vivo assay.
In animal studies atorvastatin neither affected male fertility, in administered doses of up to 175 mg/kg a day, nor female fertility, in administered doses of up to 225 mg/kg a day, and did not cause malformation.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
Mannitol.
Cellulose microcrystalline.
Crospovidone.
Sodium carbonate anhydrous.
Povidone.
Methionine.
Magnesium stearate.

Coating:
Hypromellose 6cP
Titanium dioxide (E 171)
Macrogol 6000
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Aluminium/aluminium blister packs.
Pack sizes:
Blisters:
Torvalipin filmcoated tablets 10 mg: 30, 100, tablets.
Torvalipin filmcoated tablets 20 mg: 30, 100, tablets.
Torvalipin filmcoated tablets 40 mg: 30, 100, tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer
Actavis Ltd.,
BLB016, Bulebel Industrial Estate,
Zejtun ZTN 3000,
MALTA

8. DATE OF REVISION OF THE TEXT
August 2020

teva
AAAM3620

AAAM3620 - Atorvastatin Calcium Crystalline All strengths -, PIL (blister packaging), Singapore

GENERAL INFORMATION			
Proof Round:	6	**Dimensions:**	190x500 mm
Origination Date:	19/08/2020	**Manuf. site:**	Actavis MT Zejtun
Originated by:	v.b.m	**Min pt size:**	8 pt
Revision Date:	12/11/2020	**SAP Code:**	
Revised by:	IG		

TECHNICAL CHECK		COLOURS/PLATES	
Date Sent:	19/08/2020	1. black	●
Resent Date:		2.	
Approval Date:		3.	
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teva
awstudio@tevapharm.com

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