Module 1.3 Summary of Product Characteristics, Labelling and Package Leaflet

Module 1.3.1 Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Trade Name: Zimostat 20 Tablets
INN: Atorvastatin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SN	Ingredient	Specification	Quantity per tablet	Overages
1	Atorvastatin	IH		-
2.	Maize Starch	B.P.		-
3	Lactose	B.P.		-
4	Microcrystalline Cellulose	B.P.		-
5.	Maize Starch	B.P.		
6.	Colloidal Anhydrous Silica	B.P.		-
7.	Magnesium Stearate	B.P.		-
8	Purified Talc	B.P.		-
9	Croscarmellose Sodium [Primellose]	B.P.		-
10.	Ethyl Cellulose	B.P.		-
11	Purified Talc	B.P.		-
12	Titanium Dioxide	B.P.		-
13	Hypromellose	B.P.		-

3. PHARMACEUTICAL FORM

Film Coated Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zimostat-20 is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults and children aged 10 years and older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

Zimostat-20 also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

Zimostat-20 is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol, and apolipoprotein B in

patients with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with Zimostat-20. The usual starting dose is 10 mg once a day. Doses should be individualised according to baseline LDLC levels, the goal of therapy, and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. Doses above 20mg/day have not been investigated in patients aged <18 years. Doses may be given at any time of day with or without food.

Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

Adults: The majority of patients are controlled with 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Children aged 10-17 years: Doses above 20mg/day have not been investigated.

Heterozygous Familial Hypercholesterolaemia

Adults: Patients should be started with 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant (eg, colestipol) may be combined with 40 mg Zimostat-20.

Children aged 10-17 years: Doses above 20mg/day and combination therapies have not been investigated.

Homozygous Familial Hypercholesterolaemia

Adults: In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of atorvastatin.

Children: Treatment experience in a paediatric population with doses of up to 80 mg/day is limited.

Dosage in Patients With Renal Insufficiency

Renal disease has no influence on the plasma concentrations nor lipid effects of atorvastatin; thus, no adjustment of dose is required.

Dosage in Patients With Hepatic Dysfunction

In patients with moderate to severe hepatic dysfunction, the therapeutic response to atorvastatin is unaffected but exposure to the drug is greatly increased. Cmax increases by approximately 16 fold and AUC (0-24) by approximately 11 fold.

Therefore, caution should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Geriatric Use

Adequate treatment experience in adults age 70 or older with doses of atorvastatin up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

4.3 Contraindications

Zimostat-20 is contraindicated in patients with hypersensitivity to any component of this medication, 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 special precautions for use

Liver Effects

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Muscle effects

Treatment with HMG-CoA reductase inhibitors (statins) has been associated with the onset of myalgia, myopathy, and very rarely rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness or muscle cramps. In such cases creatine kinase (CK) levels should be measured.

Creatine phosphokinase measurement

Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline >5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Before treatment

As with other statins atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine phosphokinase (CPK) level should be measured before starting treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age> 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis

In such situations, the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CPK levels are significantly elevated >5 times ULN) at baseline, treatment should not be started.

Whilst on treatment

- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK levels should be measured. If these levels are found to be significantly elevated > 5 times ULN), treatment should be stopped.

- If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to 5 times ULN, treatment discontinuation should be considered.

- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.

The risk of myopathy during treatment with atorvastatin may be increased with concurrent administration of certain other drugs, such as fibrates (e.g. gemfibrozil) and co-administration should only be undertaken with caution. (See Interaction with other medicaments and other forms of interaction).

As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported.

Children aged 10-17 years

In patients aged <18 years efficacy and safety have not been studied for treatment periods>52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, azole antifungals, or niacin. This increase in risk may also occur when combining these drugs with atorvastatin..

Phenazone (antipyrine) is a non-specific model for evaluation of drug metabolism by the hepatic microsomal enzyme system. Administration of multiple doses of atorvastatin with phenazone showed little or no detectable effect on the pharmacokinetics of phenazone in healthy subjects (no change in the clearance of phenazone but the formation clearance of 4-hydroxyphenazone increased by 20% and that of norphenazone by 8%).

More specific in vitro studies using human hepatic microsomes and cells expressing human cytochrome P450 isozymes show that atorvastatin, like other HMG-CoA reductase inhibitors, is metabolised by cytochrome P450 3A4 indicating the possibility of an interaction with drugs also metabolised by this isozyme. When combining atorvastatin with other drugs which are the substrate of this isozyme (eg, immunomodulators, many antiarrhythmic agents, some calcium channel antagonists and some benzodiazepines) the possibility of a change in the plasma drug levels of either drug should be considered. In clinical studies in which atorvastatin was administered with antihypertensives (including ACE inhibitors, beta-blockers, calcium channel antagonists, and diuretics) or hypoglycaemic agents no clinically significant interactions were seen.

Based on experience with other HMG-CoA reductase inhibitors caution should also be exercised when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (eg, certain macrolide antibiotics and azole antifungals). Increases and decreases in plasma phenytoin levels have been reported, but the relationship with atorvastatin is unknown.

Inhibitors of P-glycoprotein: Atorvastatin and atorvastatin metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. cyclosporin) can increase the bioavailability of atorvastatin and thereby increase the risk of dose-related side-effects such as myopathy.

Gemfibrozil/fibric acid derivatives: The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse event has been described when fibrates are co-administered with HMG-CoA reductase inhibitors. The risk of atorvastatin induced myopathy may therefore be increased with concomitant use of fibric acid derivatives. Pre-clinical data suggest that gemfibrozil may also interact with atorvastatin by inhibiting its glucuronidation. Co-administration of atorvastatin with fibrates (especially gemfibrozil) should only be undertaken with caution.

Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Erythromycin, clarithromycin: Coadministration of atorvastatin and erythromycin (500 mg QID), or clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin.

Azithromycin: Coadministration of atorvastatin and azithromycin (500 mg OD) did not alter the plasma concentrations of atorvastatin.

Oral contraceptives: Administration of atorvastatin with an oral contraceptive containing norethisterone and ethinyl oestradiol produced increases in plasma concentrations of norethisterone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Amlodipine: Atorvastatin pharmacokinetics were not altered by the coadministration of amlodipine 10 mg at steady state.

Colestipol: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were administered together than when either drug was given alone.

Antacid: Administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDLC reduction was not altered.

Warfarin: Administration of atorvastatin with warfarin caused a minimal decrease in prothrombin time (mean ± SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg atorvastatin. Dosing continued for 15 days and prothrombin time returned to normal by the end of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Cimetidine: An interaction study with cimetidine and atorvastatin was conducted, and no interaction was seen.

Grapefruit juice: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37 % and a decreased AUC of 20.4 % for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.

Protease inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with an approximately two-fold increase in plasma concentrations of atorvastatin. Consideration should be given to starting atorvastatin at a lower dose (see section 4.2) when co-administered with a protease inhibitor.

4.6 Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.

An interval of 1 month should be allowed from stopping atorvastatin treatment to conception in the event of planning a pregnancy.

In animal studies atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin equivalent to 6 and 21 times that expected in man, respectively.

In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether this drug or its metabolites is excreted in human milk.

4.7 Effects on ability to drive and use machines

There is no reported adverse events suggesting that patients taking atorvastatin will have any impairment of ability to drive and use hazardous machinery.

4.8 Undesirable effects

Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to atorvastatin.

The most frequent (1% or more) adverse effects associated with atorvastatin therapy, in patients participating in controlled clinical studies were:

Psychiatric Disorders: insomnia

Nervous System Disorders: headache

Gastrointestinal Disorders: abdominal pain, dyspepsia, nausea, flatulence, constipation, diarrhoea

Musculoskeletal and Connective Tissue Disorders: myalgia

General Disorders and Administration Site Conditions: asthenia

Elevated serum ALT levels have been reported in 1.3% of patients receiving atorvastatin. Clinically important (>3 times upper normal limit) elevations in serum ALT levels occurred in about 0.8% patients on atorvastatin. It was dose related and was reversible in all

Elevated serum CPK levels (>3 times upper normal limit) occurred in 2.5% patients on atorvastatin compared with 3.1% with other HMGCoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in only 0.4% atorvastatin-treated patients. Only 0.1% patients had concurrent muscle pain, tenderness, or weakness.

Additional adverse events that have been reported in atorvastatin clinical trials are categorised below according to system organ class and frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%), rare (>0.01% and <0.1%) and very rare (<0.01%).

Metabolism and Nutrition Disorders
anorexia - uncommon
hypoglycaemia - very rare
hyperglycaemia - very rare

Nervous system Disorders
dizziness - common
paresthesia - uncommon
peripheral neuropathy - rare

Gastrointestinal Disorders
vomiting - uncommon
pancreatitis - rare

Hepatobiliary Disorders
hepatitis - very rare
cholestatic jaundice - very rare

Skin and Subcutaneous Tissue Disorders
alopecia - uncommon
pruritis - uncommon
rash - uncommon

Musculoskeletal and Connective Tissue Disorders
muscle cramps - uncommon
myositis - rare
myopathy - very rare

Reproductive System and Breast Disorders
impotence - uncommon

General Disorders and Administration Site Conditions
chest pain - common
angina - common
angioneurotic oedema - very rare

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL, IDL, LDL and VLDL fractions.

Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol, LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia, a population that rarely responds to other lipid-lowering medications.

A variety of clinical studies have demonstrated that elevated levels of total-Cholesterol, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin reduces total cholesterol (total-C), LDL cholesterol (LDL-C) and apo B in patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL cholesterol (VLDL-C) and triglycerides (TG) and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridermia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia. The effect of atorvastatin on cardiovascular morbidity and mortality has not been determined.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the

independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

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5.2 Pharmacokinetic properties

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is 98% bound to plasma proteins.

Metabolism: Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated 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.

Excretion: Atorvastatin and atorvastatin metabolites are substrates of P-glycoprotein. Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMGCoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Paediatric: Pharmacokinetic data in the paediatric population are not available.

Gender: Concentrations of atorvastatin in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11fold in AUC) in patients with chronic alcoholic liver disease (Childs Pugh B).

5.3 Preclinical safety data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8 to 16fold 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 dose used, and the maximum dose used was 250 fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6 to 11fold higher based on AUC (0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Lactose
Microcrystalline Cellulose
Colloidal Anhydrous Silica
Magnesium Stearate
Purified Talc
Isopropyl Alcohol
Acetone
Propylene Glycol
Ethylcellulose
Titanium Dioxide
Hypromellose

6.2 Incompatibilities

None

6.3 Shelf life

36 months from the date of manufacture

6.4 Special precautions for storage

Store in a cool dry place protected from light

6.5 Nature and contents of container

10 tablets in a blister pack
10 blister packs in a carton

6.6 Instructions for use and handling

No special requirement

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable