SUMMARY OF PRODUCT CHARACTERISTICS

1-Name of the Medicinal Product:

1.1 Product Name

Lipiduce 10mg Film-Coated Tablet

1.2 Strength

Each Tablet contains Atorvastatin Calcium equivalent to Atorvastatin 10mg.

1.3 Pharmaceutical Dosage Form

Oral solid dose

2-Quality and Quantitative Composition:

ACTIVE INGREDIENT	Per Tablet
Atorvastatin Calcium	10mg

3-Pharmaceutical Form:

White coloured film coated oval shaped tablet, shallow convex faces, plain on both sides.

4-Clinical Particulars

4.1 Therapeutic indications

Atorvastatin is indicated:

As an adjunct therapy to diet to reduce elevated total cholesterol, LDL-cholesterol, apolipoprotein B, triglycerides and increase HDL-cholesterol in patients with:

-Primary hypercholesterolemia (heterozygous familial and nonfamilial)
-Combined hyperlipidemia (Fredrickson Types IIa and IIb).
-Hypertriglyceridemia (Fredrickson Type IV).
-Primary dysbetalipoproteinemia (Fredrickson Type III)

As an adjunct therapy with other lipid lowering treatment (e.g. LDL apheresis) in homozygous familial hypercholesterolemia to reduce total cholesterol and LDL cholesterol.

4.2 Posology and method of administration

Usual Adult and adolescent dose: Oral, the recommended initial dose of atorvastatin is 10 mg once daily which may be adjusted at intervals of 4 weeks. The dosage range is 10 to 80 mg once daily.

Usual pediatric dose: Dosage has not been established. The patient should be placed on a standard cholesterol lowering diet and weight reduction programs/exercises before receiving atorvastatin and should continue the regimen during treatment with atorvastatin.

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 should be avoided.

In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary employed.

In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

4.3 Contraindications

- Active liver disease or unexplained persistent elevations of serum transaminases.
- Hypersensitivity to any component of this drug
- Pregnancy and lactation

4.4 Special warning and precautions for use

- Skeletal Muscle Effects: Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (> 1g/day) should carefully weight the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weaknesses, particularly during the initial months of therapy and during any periods of upwards dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy.
- There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:
    - Persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.
    - Muscle biopsy showing necrotizing myopathy without signification inflammation
    - Improvement with immunosuppressive agents.
- Liver dysfunction: HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. Therefore, liver function tests should be performed prior to any at 12 weeks following initiation of therapy or elevation in dose, and semiannually thereafter.

- Atorvastatin should used with caution inpatients with alcoholism, organ transplant with immunosuppressant therapy and/or patients who have a history of liver disease.
- Serious conditions such as hypotension, severe acute infection, severe metabolic, endocrine, or electrolyte disorder, uncontrolled seizures, major surgery, or trauma may increased risk of secondary renal failure if rhabdomyolysis occurs.

4.5 Interaction with other medicinal products

Concurrent use of fibrates may cause severe myositis and myoglobinuria: The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin or cytochrome P450 3A4 inhibitors (eg erythromycin and azole antifungals).

Inhibitors of cytochrome P450 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Transporter Inhibitors: Atorvastatin and atorvastatin metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin.

Erythromycin/Clarithromycin: Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin.

Protease inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride: Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

Cimetidine: No clinically significant interactions were seen.

Itraconazole: Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC.

Grapefruit juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Inducers of cytochrome P450 3A: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg 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 atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

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 co-administered than when either drug was given alone.

Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were co-administered, 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.

Azithromycin: Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

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 contraceptive for a woman taking atorvastatin.

Warfarin: Co-administration of atorvastatin 80mg daily with warfarin will cause small decrease in prothrombin time and increase bleeding time. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs.

Amlodipine: Co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

Colchicine: Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Fusidic Acid: Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate

Other Concomitant Therapy: Atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted

4.6 Pregnancy and lactation

Atorvastatin is not recommended during pregnancy, in women who plan to become pregnant in the near future, or during lactation.

4.7 Effects on ability to drive and use machine

Not known.

4.8 Undesirable effects

Myalgia, myositis, rhabdomyolysis, constipation, diarrhea, heartburn, stomach pain, dizziness, headache, nausea, skin rash, insomnia.

Musculoskeletal disorders
Frequency not known:
Immune-mediated necrotizing myopathy

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 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

4.9 Overdose

There is no specific treatment of atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5-Pharmacological Properties :

5.1 Pharmacodynamic properties

Atorvastatin is a selective, competitive inhibitor of 3-Hydroxy- 3-methylglutaryl coenzyme A (HMG-CoA) reductase. The inhibition of HMG-CoA reductase prevents conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Inhibition of cholesterol synthesis in the liver leads to upregulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. It may also reduce the production of LDL as a result of inhibition of hepatic synthesis of very low-density lipoprotein (VLDL), the precursor of LDL.

HMG-CoA reductase inhibitors reduce LDL-cholesterol, VLDL-cholesterol, and to a lesser extent, plasma triglyceride concentrations, and slightly increase high-density lipoprotein (HDL) concentration.

5.2 Pharmacokinetic properties

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentration occurs within 1 to 2 hours. It has low absolute bioavailability of about 12% due to presystemic clearance in the gastrointestinal mucosa and / or first-pass metabolism in the liver, its primary sites of action.

Atorvastatin is 98% bound to plasma proteins. It is metabolized by ortho- and parahydroxylation and beta- oxidation to active metabolites. The drug and its metabolites are eliminated primarily in the bile. The mean plasma elimination half-life is approximately 14 hours

6-Pharmaceutical Particulars:

6.1 List of excipients

Lactose Monohydrate
Microcrystalline Cellulose
Calcium Carbonate
Croscarmellose Sodium
Polysorbate 80
Polyvinylpyrrolidone
Magnesium stearate

Coating:
Hydroxypropyl methylcellulose E5
Hydroxypropyl methylcellulose E15
Titanium Dioxide
Talc
Propylene Glycol

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Proposed 3 years

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

Descriptions of each packaging material for Lipiduce-10mg Tablet is as below:

Primary Packaging

Blister pack

Type

Push-through blister pack; the package consists of a clear thermoformable plastic (PVDC) material and a heat-sealed, lacquered backing material.

Cold-form blister foil

Description	:	Multilayer cold-form aluminium-based blister foil, with a composition comprising nylon/Aluminium/PVC
Appearance	:	Bright surface/Matt surface each side

Aluminium blister foil

Description	:	Aluminium foil with high slip primer on bright surface and heat seal on matt surface/ Aluminium foil with high slip primer on matt surface and heat seal on bright surface
Appearance	:	Bright surface/Matt surface each side

Outer Container / Secondary Packaging

Outer Container/Packaging

Type: Unit box, Package Insert & Plain Carton for Hovid-Lipiduce 10 Tablet

6.6 Special precautions for disposal

Not Applicable

7-Marketing Authorization Holder:

Name	:	HOVID Bhd.
Address	:	121, Jalan Tunku Abdul Rahman, (Jalan Kuala Kangsar) 30010 Ipoh, Perak, Malaysia

8-Manufacturer Name:

Production Site/Final Release Address	**:**	HOVID Bhd. Lot 56442, 7 ½ Miles, Jalan Ipoh / Chemor, 31200 Chemor, Malaysia.

9-Date of revision of the text :

April 2023

10-Instruction for preparation of Radiopharmaceuticals (If applicable):

Not Applicable