Clean Proposed Professional Information

SCHEDULING STATUS S4

1. NAME OF THE MEDCINE

LIPOGEN 10 (Film-coated tablets)

LIPOGEN 20 (Film-coated tablets)

LIPOGEN 40 (Film-coated tablets)

LIPOGEN 80 (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LIPOGEN 10: Each film-coated tablet contains atorvastatin calcium trihydrate equivalent to atorvastatin 10 mg.

LIPOGEN 20: Each film-coated tablet contains atorvastatin calcium trihydrate equivalent to atorvastatin 20 mg.

LIPOGEN 40: Each film-coated tablet contains atorvastatin calcium trhydrate equivalent to atorvastatin 40 mg.

LIPOGEN 80: Each film-coated tablet contains atorvastatin calcium trihydate equivalent to atorvastatin 80 mg.

Antioxidants: Butylated hydroxyanisole and butylated hydroxytoluene.

Excipients with known effect:

Contains sugar: lactose monohydrate.

LIPOGEN 10: lactose monohydrate 38, 36 mg

LIPOGEN 20: lactose monohydrate 76,69 mg

LIPOGEN 40: lactose monohydrate 153,38 mg

LIPOGEN 80 : lactose monohydrate 306,76 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

LIPOGEN 10: White to off-white, film-coated, oval shaped tablets imprinted with **'A 30'** on one side and plain on the other side.

LIPOGEN 20: White to off-white, film coated, oval shaped tablets imprinted with **'A 31'** on one side and plain on the other side.

LIPOGEN 40: White to off-white, film coated, oval shaped tablets imprinted with **'A 32'** on one side and plain on the other side.

LIPOGEN 80: White to off-white, film coated, oval shaped tablets imprinted with **'A 33'** on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

(a) Hypercholesterolaemia

LIPOGEN is indicated:

1. As an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels in patients with primary hypercholesterolaemia (heterozygous familial) and mixed dyslipidaemia (Fredrickson Types IIa and IIb);
2. To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

(b) Paediatric Patients (10-17 years of age)

LIPOGEN is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, >10 to 17 years of age, with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥ 4,98 mmol/L (190 mg/dL) or

b. LDL-C remains ≥ 4,04 mmol/L (160 mg/dL) and:

- there is a positive family history of premature cardiovascular disease or
- two or more other CVD risk factors are present in the paediatric patient.

(c) Prevention of Cardiovascular Complications

In patients without clinically evident cardiovascular disease, and with or without dyslipidaemia, but with multiple risk factors for coronary heart disease such as smoking, hypertension, diabetes, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:

- reduce the risk of ischaemic cardiovascular and cerebrovascular diseases.

Secondary Prevention

LIPOGEN is indicated in the prevention of cardiovascular events in patients with clinically evident coronary heart disease and increased cholesterol levels.

Therapy with LIPOGEN should be a component of multiple-risk-factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia. LIPOGEN should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other non-pharmacological measures has been inadequate.

Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C and TG.

4.2 Posology and method of administration

Patients should be on standard cholesterol-lowering diets prior to initiation of treatment with LIPOGEN and they should remain on such diets during treatment with LIPOGEN. The usual LIPOGEN starting dose is 10 mg once daily. Doses need to be individualised based on the patient's baseline LDL-C levels, the goal of therapy and the patient's response to therapy. Dosages should only be adjusted after an interval of 4 weeks or more. The indication will determine the maximum recommended dose (see below). LIPOGEN can be taken any time of the day with or without food.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia:

Most patients are controlled on LIPOGEN 10 (10 mg) once daily. Although a therapeutic response is evident within 2 weeks of initiation of therapy, it usually takes 4 weeks to achieve maximum response. The response is sustained during chronic therapy.

Heterozygous familial hypercholesterolaemia in paediatric patients (> 10-17 years of age):

Treatment should be initiated with LIPOGEN 10 mg daily. The maximum recommended dose is 20 mg/day.

Homozygous familial hypercholesterolaemia in adults:

In a compassionate-use, uncontrolled trial in which 29 patients with homozygous familial hypercholesterolaemia participated, most patients responded to a 80 mg atorvastatin dose, with a mean reduction in LDL-C of 20 % (range 7 % - 53 %). However, some patients experienced an increase in LDL-C.

Prevention of cardiovascular complications:

The dosage range is 10-80 mg once daily.

Special populations

Dosage in patients with renal insufficiency:

No dose adjustment is required in patients with renal disease, since renal disease does not influence the plasma concentrations nor the lipid effects of LIPOGEN.

Dosage in patients with hepatic dysfunction:

Although the therapeutic response to LIPOGEN is not affected, serum levels of atorvastatin are greatly increased in patients with moderate to severe hepatic dysfunction. Patients with chronic alcoholic liver disease demonstrate markedly increased plasma concentrations of LIPOGEN. In patients with Child-Pugh A disease there is a 4-fold increase in C_{max} and AUC, while C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B disease. Caution with dosage is therefore required in patients who consume substantial quantities of alcohol and/or have a history of hepatic disease (see sections 4.3 and 4.4).

Method of administration

Oral use.

LIPOGEN can be taken any time of the day, with or without food.

4.3 CONTRAINDICATIONS

LIPOGEN is contra-indicated in:

- Patients with hypersensitivity to atorvastatin or to any component of LIPOGEN listed in section 6.1
- Patients with active liver disease or persistent elevations of serum transaminases exceeding three times the upper limit of normal.
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6)
- Patients who concomitantly use rifampicin, diltiazem and grapefruit juice.
- Patients with Child-Pugh B and C liver cirrhosis.
- Patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Liver effects:

Statins like LIPOGEN have been associated with biochemical abnormalities of liver function. **Persistent elevations [> 3 times the upper limit of normal (ULN) which occurred on 2 or more occasions] in serum transaminases occurred at incidences of 0,2 %, 0,2 %, 0,6 % and 2,3 % for 10, 20, 40 and 80 mg atorvastatin, respectively**.

Upon dose reduction, interruption of treatment, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Jaundice has been reported in patients treated with atorvastatin, as in LIPOGEN.

There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin as in LIPOGEN.

It is recommended that patients undergo liver functions tests before commencement of treatment, following each increase in dosage, and periodically thereafter. Changes in liver enzyme values mostly commence in the first 4 months of treatment with LIPOGEN. Patients who develop increases in transaminase levels require monitoring until the abnormalities have resolved. It is recommended that LIPOGEN be withdrawn if increases in ALT or AST of > 3 times ULN persist. If serious liver injury with clinical symptoms and/or

hyperbilirubinaemia or jaundice occurs during treatment with LPOGEN, promptly interrupt therapy. If an alternate aetiology is not found, do not restart LIPOGEN.

LIPOGEN should be administered with caution to patients who consume substantial quantities of alcohol and/or have a history of liver disease. Use of LIPOGEN is contra-indicated in patients with active liver disease or unexplained persistent transaminase elevations.

Haemorrhagic stroke / use in patients with recent stroke or transient ischaemic attack (TIA):

Post-hoc analysis of a clinical study indicated that patients without coronary heart disease (CHD) who had a stroke or transient ischaemic attack (TIA) within the preceding 6 months of starting atorvastatin , as in LIPOGEN had a higher incidence of haemorrhagic stroke compared to patients who received placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Skeletal muscle:

LIPOGEN**,** like other HMG-CoA reductase inhibitors may affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

There have been reports of rhabdomyolysis with or without renal impairment in patients who took HMG-CoA reductase inhibitors, such as LIPOGEN**. Rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin, as in LIPOGEN and with other statins.** A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Before the treatment

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK levelshould 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

– 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.

Creatine kinase measurement

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

Whilst on treatment

– Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

– If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK 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 the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered

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

– LIPOGEN must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysisis diagnosed or suspected.

A diagnosis of myopathy should be considered in any patient who presents with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report any of the following symptoms: unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise

or fever. If markedly elevated CPK levels occur or if myopathy is diagnosed or suspected, treatment with LIPOGEN should be discontinued.

Concomitant treatment with other medicinal products

Risk of rhabdomyolysis/myopathy is increased when LIPOGEN is administered concomitantly with certain medicines that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc).

The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products

Co-administration of immunosuppressive medicines, including ciclosporin, gemfibrozil and other fibric acid derivatives, 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, nicotinic acid / niacin, ezetimibe, azole antifungals or erythromycin and cytochrome P450 inhibitors (see section 4.5) increases the risk of myopathy during LIPOGEN treatment. Medical practitioners considering combined therapy with LIPOGEN 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 medicine. If possible, alternative (non-interacting) therapies should be considered instead of these medicines.

In cases where co-administration of these medicines with LIPOGEN is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicines that increase the plasma concentration of atorvastatin, a lower maximum dose of LIPOGEN is recommended. In addition, in the

case of potent CYP3A4 inhibitors, a lower starting dose of LIPOGEN should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

The concurrent use of LIPOGEN and fusidic acid is not recommended, and therefore, temporary suspension of LIPOGEN may be considered during fusidic acid therapy. In patients where the use of systemic fusidic acid is considered essential, LIPOGEN treatment should be discontinued throughout the duration of fusidic acid treatment. LIPOGEN therapy may be re-introduced seven days after the last dose of fusidic acid.

Lower starting and maintenance doses of LIPOGEN should be considered when taken concomitantly with the aforementioned medicines. 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.

Prescribing recommendations for interacting medicines are summarised in the table below (see also section 4.5).

Table 1: Interactions associated with increased risk of myopathy/rhabdomyolysis.

Interacting medicine	Prescribing Recommendations
CYP3A4 inhibitors Ciclosporin,telithromycin, clarithromycin, delavirdine, tiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatment of HCV (e.g., elbasvir/grazoprevir),	Avoid LIPOGEN
HIV protease inhibitors including ritonavir, lopinavir, atazanavir,indinavir, darunavir, etc.)	Should be avoided if possible. In cases where co-administration of these medicinal products with LIPOGEN cannot be avoided, lower dose is necessary, and clinical monitoring of the patient is recommended.
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir).	Do not exceed 20 mg LIPOGEN daily.
HIV protease inhibitor (nelfinavir).	Do not exceed 40 mg LIPOGEN daily.
* 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 LIPOGEN with colchicine.

If a patient presents with an acute, serious condition suggestive of myopathy, treatment with LIPOGEN should be discontinued. This also holds true for any patient with an increased risk for the development of renal failure secondary to rhabdomyolysis (e.g. patients with severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Protease inhibitors

Concomitant administration of LIPOGEN and protease inhibitors is associated with increases in LIPOGEN plasma concentrations. The concomitant use of higher doses of LIPOGEN with HIV protease inhibitors increases the risk of myopathy/rhabdomyolysis.

Endocrine function

Statins like LIPOGEN interfere with cholesterol synthesis and might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin as in LIPOGEN does not reduce basal plasma cortisol concentration or impair adrenal reserve. Caution should be exercised if LIPOGEN is administered concomitantly with medicines that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Diabetes mellitus

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin as in LIPOGEN.

Statins as a class may raise blood glucose levels and in some patients at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically.

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected that a patient has developed interstitial lung disease, LIPOGEN therapy should be discontinued.

Myasthenia gravis

Risk of myasthenia gravis and ocular myasthenia associated with use of statin containing medicines (see section 4.8).

Paediatric population

No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessmentof overall maturation and development, assessment of Tanner Stage, and measurement of height and weight (see section 4.8).

Use in the elderly

Since advanced age (≥ 65 years) is a predisposing factor for myopathy, LIPOGEN should be prescribed with caution in the elderly.

Hepatic impairment

LIPOGEN is contra-indicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels (see section 4.3).

Excipients:

LIPOGEN tablets contain lactose as an excipient and therefore, patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption, should not take LIPOGEN.

Contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin

Co-administration of LIPOGEN with immunosuppressive medicines, fibric acid derivatives, niacin (nicotinic acid) in lipid-modifying doses, or cytochrome P450 3A4 inhibitors (ciclosporin, macrolide antibiotics, e.g. clarithromycin or erythromycin and azole antifungals, and HIV protease inhibitors) increases the risk of myopathy (see section 4.4).

Inhibitors of cytochrome P450 3A4:

Since LIPOGEN is metabolised by cytochrome P450 3A4 (CYP3A4), co-administration of LIPOGEN with cytochrome P450 3A4 inhibitors can cause increases in LIPOGEN plasma concentrations. The variability of effect on cytochrome P450 3A4 determines the extent of interaction and potentiation of effects (see section 4.4).

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicines with LIPOGEN cannot be avoided lower starting and maximum doses of LIPOGEN should be considered and appropriate clinical monitoring of the patient is recommended.

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with LIPOGEN may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of LIPOGEN should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

Erythromycin / clarithromycin:

In healthy individuals, LIPOGEN plasma concentrations increased approximately 40 % with concurrent administration of erythromycin, a known inhibitor of cytochrome P450 3A4. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone. Therefore, in patients taking clarithromycin, caution should be used when the LIPOGEN dose exceeds 20 mg (see section 4.4)

Combination of protease inhibitors:

Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin as in LIPOGEN with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Co-administration of atorvastatin (40 mg once daily) with ritonavir (400 mg twice daily)

plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Co-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 4.4). Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPOGEN should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPOGEN and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of LIPOGEN should not exceed 20 mg and should be used with caution (see section 4.4). In patients taking the HIV protease nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of LIPOGEN should not exceed 40 mg and close clinical monitoring is recommended.

Diltiazem hydrochloride:

Concurrent administration of LIPOGEN with diltiazem is associated with a 51 % increase in the AUC of LIPOGEN (see section 4.3).

Cimetidine:

Co-administration of LIPOGEN and cimetidine does not alter atorvastatin plasma concentrations or LDL-C reductions.

Grapefruit juice:

One or more components of grapefruit juice inhibit CYP 3A4 and can cause increases in plasma concentrations of LIPOGEN by a factor of 2,5 to 3,5. This combination should therefore be avoided (see section 4.3).

Itraconazole:

Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the LIPOGEN dose exceeds 20 mg.

Ticagrelor:

Co-administration of LIPOGEN and ticagrelor increased atorvastatin acid Cmax by 23% and AUC by 36%. Similar increases in AUC and Cmax were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Inducers of cytochrome P450 3A4:

Co-administration of LIPOGEN with medicines that induce cytochrome P450 3A4 (e.g. efavirenz, rifampicin, St. John's Wort) can cause variable reductions in plasma concentrations of LIPOGEN Due to the dual interaction mechanism of rifampicin (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of LIPOGEN with rifampicin is not recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampicin on atorvastatin concentrations in hepatocytes is however unknown. The concomitant administration of LIPOGEN and rifampicin is contra-indicated.

Antacid:

Concurrent administration of oral antacid suspensions that contain magnesium and aluminium hydroxides with LIPOGEN will reduce plasma concentrations of atorvastatin by approximately 35 %. However, this does not alter the extent of LDL-C reduction.

Antipyrine:

Because LIPOGEN does not affect the pharmacokinetics of antipyrine, interactions with other medicines metabolised via the same cytochrome isozymes are not expected

Colestipol:

Concomitant administration of colestipol and LIPOGEN will reduce LIPOGEN plasma concentrations with approximately 25 %. However, the reduction in LDL-C is greater when LIPOGEN and colestipol is given concurrently than when either medicine is administered alone.

Digoxin:

Concurrent administration of multiple doses of LIPOGEN and digoxin can increase steady-state digoxin plasma concentrations by approximately 20 %. Patients receiving digoxin need to be monitored appropriately (see section 4.4)

Azithromycin:

Concurrent administration of LIPOGEN (10 mg once daily) and azithromycin (500 mg once daily) does not change the plasma concentrations of atorvastatin.

Oral contraceptives:

When LIPOGEN is co-administered with an oral contraceptive, increases in AUC values of norethindrone and ethinyl oestradiol of approximately 30 % and 20 %, respectively, may occur. These increases should be taken into account when an oral contraceptive is selected for a woman on LIPOGEN.

Warfarin:

Prothrombin time/INR should be determined before starting LIPOGEN in patients taking anticoagulants such as warfarin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time/INR occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on anticoagulant therapy. If the dose of LIPOGEN is changed or discontinued, the same procedure should be repeated. Patients receiving LIPOGEN should be closely monitored when LIPOGEN is combined with warfarin therapy.

Amlodipine:

Co-administration of LIPOGEN 80 mg and amlodipine 10 mg does not alter LIPOGEN pharmacokinetics at steady state.

Other concomitant therapy:

No evidence of clinically significant adverse interactions have been reported when atorvastatin, such as contained in LIPOGEN was used concomitantly with antihypertensive medicines and oestrogen replacement therapy. However, interaction studies with specific medicines have not been performed.

Ciclosporin / transport protein inhibitors:

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 / transport proteins (e.g. ciclosporin) can increase the bioavailability of atorvastatin. The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and ciclosporin 5,2 mg/kg/day compared to that of atorvastatin alone. The co-administration of LIPOGEN with ciclosporin should be avoided.

Gemfibrozil:

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of LIPOGEN with gemfibrozil should be avoided (see section 4.4).

Other fibrates / fibric acid derivatives:

The use of fibrates alone is occasionally associated with muscle related events, including myopathy / rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and LIPOGEN. If concomitant administration cannot be avoided, the lowest dose of LIPOGEN to achieve the therapeutic objective should be used and the patients should be appropriately monitored.

Ezetimibe:

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and LIPOGEN Appropriate clinical monitoring of these patients is recommended.

Fusidic acid:

Interaction studies with LIPOGEN and fusidic acid have not been conducted. Muscle related events, including rhabdomyolysis, have been reported with atorvastatin as in LIPOGEN and fusidic acid when given concurrently. The mechanism of this interaction is not known. The concurrent use of LIPOGEN and fusidic acid is not recommended, and therefore, patients should be closely monitored and temporary suspension of LIPOGEN treatment may be appropriate.

Niacin:

The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin; a reduction in LIPOGEN dosage should be considered in this setting.

Colchicine:

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

Paediatric population

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

LIPOGEN is contra-indicated in pregnancy and lactation as well as in women of childbearing potential who are not making use of adequate contraception. LIPOGEN should be administered to women of childbearing age only when such patients are using adequate contraception and have been informed of the potential hazards to the foetus. If a pregnancy is being planned, an interval of one month should be allowed from discontinuing LIPOGEN treatment to conception.

Breastfeeding

Women who are breastfeeding should be advised to not use LIPOGEN. Patients who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

Fertility

It is reported that atorvastatin had no effect on male or female fertility.

4.7 Effects on ability to drive and use machines:

LIPOGEN has negligible influence on the ability to drive and use machines. However, LIPOGEN may cause dizziness and blurred vision that can impair a patient's ability to drive or use machinery.

4.8 Undesirable Effects

MedRA System organ class	**Frequency**	**Adverse Effects**
Infections and infestations		
	Frequent	Nasopharyngitis.
Blood and lymphatic system disorders		
	Less frequent:	Thrombocytopenia.
Immune system disorders		
	Frequent	Allergic reactions.
	Less frequent:	Anaphylaxis, angioedema.
Metabolism and nutrition disorders		
	Frequent	Hyperglycaemia, HbA1c glycosylated haemoglobin increases
	Less frequent:	Hypoglycaemia, weight gain, anorexia.
	Unknown frequency	Diabetes mellitus
Psychiatric disorders		

	Less frequent	Nightmare, insomnia.
	Unknown frequency:	Depression, cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion).
Nervous system disorders		
	Frequent	Headache.
	Less frequent	Dizziness, paraesthesia, hypoaesthesia, dysgeusia, amnesia, peripheral neuropathy, haemorrhagic stroke (see section 4.4**)**
	Frequency unknown	Myasthenia gravis
Eye disorders		
	Less frequent	Blurred vision, visual disturbance
	Frequency unknown	Ocular myasthenia
Ear and labyrinth disorders		
	Less frequent	Tinnitus, hearing loss
Respiratory, thoracic and mediastinal disorders		
	Frequent	Pharyngolaryngeal pain, epistaxis.
	Unknown frequency	Interstitial lung disease (see section 4.4)

Gastro-intestinal disorders		
	Frequent	Constipation, flatulence, dyspepsia, nausea, diarrhoea
	Less frequent	Vomiting, upper and lower abdominal pain, eructation, pancreatitis
	Unknown frequency	Abdominal discomfort.
Hepatobiliary disorders		
	Less frequent	Hepatitis, cholestasis, jaundice, hepatic failure.
Skin and subcutaneous tissue disorders		
.	Less frequent	Urticaria, skin rash, pruritus, alopecia, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders		
	Frequent	Myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain

	Less frequent	Neck pain, muscle fatigue, myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture
	Unknown frequency	Musculoskeletal pain.
Renal and urinary disorders		
	Unknown frequency	Urinary tract infection
Reproductive system and breast disorders		
	Less frequent	Gynaecomastia
	Unknown frequency	Sexual dysfunction
General disorders and administration site conditions		
	Less frequent	Malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.
Investigations		
	Frequent	Abnormal liver function test, increased blood creatine kinase
	Less frequent	Positive white blood cells urine.
	Frequency unknown:	Increased blood alkaline phosphatase, increase hepatic enzyme, elevated hepatic/serum transaminases (including increase alanine aminotransferase), elevated

		serum creatine kinase (CK) levels (see section 4.4).

Description of selected adverse reactions

Paediatric patients (ages 10-17 years)

The most frequent adverse reactions are infections.

Other frequent adverse events reported in children are headache, abdominal pain, increased alanine aminotransferase, increased blood creatine phosphokinase.

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 limited experience with respect to long-term safety in the paediatric population.

4.9 Overdose

There is no specific treatment for overdosage with LIPOGEN. Should an overdose occur, symptomatic and supportive measures should be instituted as required. Liver function tests should be performed and serum CK levels should be monitored. Since atorvastatin is extensively bound to plasma proteins, haemodialysis is not expected to significantly contribute to LIPOGEN clearance.

5. PHARMACOLOGICAL ~~ACTION~~ PROPERTIES

5.1 Pharmacodynamic properties

Category A, class 7.5 Serum-cholesterol reducers.

Pharmacotherapeutic group:

Lipid modifying agents, HMG-CoA- reductase inhibitors, ATC code: C10AA05.

Atorvastatin selectively and competitively inhibits HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate. Mevalonate is a precursor of sterols, including cholesterol.

Atorvastatin's primary site of action is the liver. The liver is also the principal site of cholesterol synthesis as well as of clearance of low-density lipoprotein cholesterol (LDL-C).

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels through inhibition of HMG-CoA reductase and hepatic synthesis of cholesterol as well as through increasing the number of LDL-C receptors on the cell-surface of hepatocytes, which provides for enhanced uptake and catabolism of LDL-C.

LDL-C production is reduced as is the number of LDL-C particles. In patients with hypercholesterolaemia, depending on the dose, atorvastatin reduces the number of apolipoprotein-B-containing particles. Atorvastatin is responsible for an increase in LDL-C receptor activity combined with a change in the quality of circulating LDL-C particles.

Atorvastatin therapy leads to a reduction in total cholesterol (total-C), LDL-C, and apolipoprotein-B in normal volunteers and in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia, mixed dyslipidaemia, and in some patients who suffer from homozygous familial hypercholesterolaemia. It also reduces serum triglyceride (TG) levels and leads to variable increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A-1 levels in patients with non-familial hypercholesterolaemia and mixed dyslipidaemias.

5.2 Pharmacokinetic properties:

Absorption:

Maximum plasma concentrations are achieved within 1 to 2 hours after oral administration. Atorvastatin (parent substance) has an absolute bioavailability of approximately 12 %, while the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. Presystemic clearance in gastrointestinal mucosa and/or

hepatic first-pass metabolism is thought to be responsible for the low systemic availability. Food reduces the rate and extent of absorption by approximately 25 % and 9 %, respectively, as assessed by C_{max} and AUC. However, the reduction in LDL-C is similar whether atorvastatin is administered with or without food. If atorvastatin is taken in the evening, plasma medicine concentrations are lower (approximately 30 % for C_{max} and AUC) compared to morning administration. However, LDL-C reduction is the same regardless of whether the medicine is administered in the morning or evening.

Distribution:

Atorvastatin has a mean volume of distribution of approximately 381 litres. Plasma protein binding of atorvastatin is 98 %.

Metabolism:

Cytochrome P450 3A4 extensively metabolises atorvastatin to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* these ortho- and parahydroxylated metabolites inhibit HMG-CoA reductase to an extent equivalent to that of atorvastatin. Active metabolites are thought to be responsible for approximately 70 % of the circulating inhibitory activity for HMG-CoA reductase.

Excretion:

Following hepatic and/or extrahepatic metabolism, atorvastatin is eliminated primarily in bile. It does not, however, appear to undergo enterohepatic recirculation. Atorvastatin (parent substance) has a mean plasma elimination half-life in humans of approximately 14 hours. Due to the contribution of active metabolites, the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours. Recovery in urine is less than 2 % of an orally administered dose of atorvastatin.

Special populations:

Elderly:

In healthy elderly subjects (65 years and older) atorvastatin plasma concentrations are higher (approximately 40 % for Cmax and 30 % for AUC) than in young adults. The extent of LDL-C reduction is similar to that observed in younger patients given equal doses of atorvastatin.

Gender:

Although there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women, plasma concentrations in women are different (approximately 20 % higher for Cmax and 10 % lower for AUC) from those observed in men.

Renal insufficiency:

Kidney disease does not influence the plasma concentrations or lipid effects of atorvastatin. Dose adjustment in patients with renal dysfunction is therefore not necessary (see section 4.2).

Haemodialysis:

No studies were performed in patients with end-stage renal disease. Due to the fact that atorvastatin is extensively bound to plasma proteins, haemodialysis is not expected to significantly enhance its clearance.

Hepatic insufficiency:

Patients with chronic alcoholic liver disease (Child-Pugh B) have markedly increased plasma concentrations of atorvastatin (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Colloidal anhydrous silica, croscarmellose sodium, hydroxy propyl cellulose-L, isopropyl alcohol, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium carbonate anhydrous, sodium lauryl sulphate and coating agent (Opadry YS-1-7040 white; Hypromellose 6 cp; Macrogol / PEG 8000; Titanium dioxide; Talc)

Antioxidants: Butylated hydroxy anisole and butylated hydroxy toluene

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from light and moisture.

Do not remove the blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Cartons containing 30 tablets packed in cold form blister strips or desiccant embedded cold form blister strips of 10 tablets each**.**

Cold form blister strips comprised of cold form blister laminate composed of aluminium foil (one side bright, soft tempered, plain; dull side lacquer-laminated to oriented polyamide film; bright side lacquer-laminated to PVC film), PVC and polyamide with a backing of aluminium foil coated with heat seal lacquer on the inner side.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

a Sun Pharma company

14 Lautre Road, Stormill, Ext. 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBERS

LIPOGEN 10 : 42/7.5/0556

LIPOGEN 20 : 42/7.5/0557

LIPOGEN 40: 42/7.5/0558

LIPOGEN 80 : 42/7.5/0559

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of registration: 04 December 2009

Date of revision: 21 May 2024

Namibia: **NS2**

LIPOGEN 10 : 19/7.5/0087
LIPOGEN 20 : 19/7.5/0088
LIPOGEN 40: 19/7.5/0089
LIPOGEN 80 : 19/7.5/0090

Botswana: **S2**

LIPOGEN 10 : BOT1703032
LIPOGEN 20 : BOT1703033
LIPOGEN 40: BOT1703034
LIPOGEN 80: BOT1703035

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