SCHEDULING STATUS S4

1 NAME OF THE MEDICINE
CHOLMIN 10 (film-coated tablets)
CHOLMIN 20 (film-coated tablets)
CHOLMIN 40 (film-coated tablets)
CHOLMIN 80 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
CHOLMIN 10: Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 10 mg atorvastatin. Contains sugar: 70,97 mg mannitol
CHOLMIN 20: Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 20 mg atorvastatin. Contains sugar: 141,94 mg mannitol
CHOLMIN 40: Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 40 mg atorvastatin. Contains sugar: 283,88 mg mannitol
CHOLMIN 80: Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 80 mg atorvastatin. Contains sugar: 567,76 mg mannitol
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
CHOLMIN 10: White coloured, oval shaped, biconvex film-coated tablets with one side embossed "10" and other side plain.
CHOLMIN 20: White coloured, oval shaped, biconvex film-coated tablets with one side embossed "20" and other side plain.
CHOLMIN 40: White coloured, oval shaped, biconvex film-coated tablets with one side embossed "40" and other side plain.
CHOLMIN 80: White coloured, oval shaped, biconvex film-coated tablets with one side embossed "80" and other side plain.

4 CLINICAL PARTICULARS
Therapeutic indications
Hypercholesterolemia
CHOLMIN is indicated:
- As an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, triglyceride levels and to moderately increase HDL-cholesterol in patients with primary hypercholesterolaemia (heterozygous familial and non-familial hypercholesterolaemia) and combined/mixed dyslipidaemia;
- 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.

Paediatric patients (10 – 17 years of age)
CHOLMIN is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and post-menarchal girls, > 10 to 17 years of age, with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy, the following findings are present:
- LDL-C remains ≥ 4,98 mmol/L (190 mg/dL) or
- 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

Reduction 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, CHOLMIN is indicated to reduce the risk of ischaemic cardiovascular and cerebrovascular diseases.
Secondary reduction
Reduction of cardiovascular events in patients with clinically evident coronary heart disease and increased cholesterol levels.
Therapy with lipid-lowering agents should be a component of multiple-risk factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia. Lipid-altering agents 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 CHOLMIN, secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease, other medicine therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C and HDL-C and TG.

Posology and method of administration
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving CHOLMIN and should continue on this diet during treatment with CHOLMIN.
The usual starting dose is 10 mg once a day and should be individualised according to the baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should only be made after an interval of 4 weeks or more. The maximum recommended daily dose will depend on the indication (see below).

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia:
The majority of patients are controlled with 10 mg CHOLMIN 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.

Heterozygous familial hypercholesterolaemia in paediatric patients (> 10 – 17 years of age):
Experience in paediatrics is limited to a small number of patients (age 10 – 17 years) with severe dyslipidaemias, such as familial hypercholesterolaemia. Patients should be started with CHOLMIN 10 mg daily, the maximum recommended dose is 20 mg/day

Homozygous familial hypercholesterolaemia:
In a compassionate-use, uncontrolled study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of CHOLMIN, with a greater than 15 % reduction in LDL-C (18 % to 45 %).

Reduction of cardiovascular complications:
The dose range is 10 to 80 mg daily.

Special populations
Dosage in patients with renal insufficiency:
Renal disease has no influence on the plasma concentration or on the lipid effects of CHOLMIN, thus no adjustment of dose is required (See section 4.4).

Dosage in patients with hepatic dysfunction:
In patients with moderate to severe hepatic dysfunction, the therapeutic response to CHOLMIN is unaffected but serum levels of the medicine are greatly increased. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Child-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B disease. Therefore, caution with dosage should be exercised in patients who consumer substantial quantities of alcohol and/or have a history of liver disease (See sections 4.3 and 4.4).

Method of administration
CHOLMIN is for oral administration.
Doses may be given at any time of day with or without food.

Contraindications
CHOLMIN is contraindicated in patients:
- with hypersensitivity to atorvastatin or to any of the excipients of CHOLMIN listed in section 6.1.
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6)
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir.
- taking rifampicin, diltiazem and drink grapefruit juice (see section 4.5)
- patients with Child-Pugh B and C (liver cirrhosis)

Special warnings and 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 transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of CHOLMIN is recommended (see section 4.8).
CHOLMIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of CHOLMIN 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Skeletal muscle effects
Atorvastatin 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 very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.
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 CHOLMIN, 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 atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- CHOLMIN must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products
Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicines that may increase the plasma concentration of atorvastatin such as colchicine, potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letemovir and HIV protease inhibitors including atazanavir, indinavir, saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir and fosamprenavir plus ritonavir and cytochrome P450 inhibitors). 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 medicines.
In cases where co-administration of these medicinal products with CHOLMIN is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of CHOLMIN should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

CHOLMIN must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of CHOLMIN and fusidic acid should only be considered on a case by case basis and under close medical supervision.
CHOLMIN therapy should be withdrawn in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CHOLMIN.
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI> 30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

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

Interaction with other medicines and other forms of interaction
Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are
substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin
(see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).

CYP3A4 inhibitors
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, some antivirals used in the treatment of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir) should be avoided if possible. In cases where co-administration of these medicinal products with CHOLMIN cannot be avoided lower starting and maximum doses of CHOLMIN 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. Whilst both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of CHOLMIN 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.

CYP3A4 inducers
Concomitant administration of CHOLMIN with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of CHOLMIN with rifampicin is not recommended, as delayed administration of atorvastatin as contained in CHOLMIN 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 and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors
Inhibitors of transport proteins (e.g. ciclosporin, letermovir) can increase the systemic exposure of atorvastatin. The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended. Use of CHOLMIN is not recommended in patients taking letermovir co-administered with ciclosporin (see section 4.4).

Gemfibrozil / fibric acid derivatives
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

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 atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered
than when either medicine was given alone.

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, CHOLMIN treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

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 CHOLMIN with colchicine.

Antacids
Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides can decrease plasma concentrations of atorvastatin, however, LDL-C reduction will not be altered.

Effect of atorvastatin on co-administered medicines
Digoxin
When multiple doses of digoxin and atorvastatin were co-administered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives
Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin
In a clinical study in patients receiving chronic warfarin therapy, co-administration of atorvastatin daily with warfarin caused a small decrease in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking warfarin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on warfarin. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

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.

Grapefruit juice
Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of CHOLMIN by 2,5 to 3,3-fold and the combination should be avoided (see section 4.3).

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
CHOLMIN is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. Maternal treatment with CHOLMIN may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, CHOLMIN should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with CHOLMIN should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3.).

Breastfeeding
It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. Because of the potential for serious adverse reactions, women taking CHOLMIN should not breast-feed their infants (see section 4.3). CHOLMIN is contraindicated during breastfeeding (see section 4.3).

Fertility
In animal studies atorvastatin had no effect on male or female fertility.

Effects on ability to drive and use machines
CHOLMIN has negligible influence on the ability to drive and use machines.

Undesirable effects
b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	Infection, flu syndrome, Nasopharyngitis
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Frequent	Allergic reactions
	Less frequent	Anaphylaxis
Metabolism and nutrition disorders	Frequent	Hyperglycaemia
	Less frequent	Hypoglycaemia, weight gain, anorexia
Psychiatric disorders	Less frequent	Nightmare, insomnia
Nervous system disorders	Frequent	Headache
	Less frequent	dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia, peripheral neuropathy
Eye disorders	Less frequent	Blurred vision, visual disturbance
Ear and labyrinth disorders	Less frequent	Tinnitus, hearing loss
Respiratory, thoracic and mediastinal disorders	Frequent	Sinusitis, pharyngitis, Pharyngolaryngeal pain, epistaxis
Gastrointestinal disorders	Frequent	Constipation, flatulence, dyspepsia, nausea, diarrhoea
	Less frequent	Vomiting, abdominal pain upper and lower, eructation, pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis, cholestasis, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Urticaria, skin rash, pruritus, alopecia, angioneurotic oedema, 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, muscle rupture, tendonopathy, sometimes complicated by rupture, lupus-like syndrome
	Frequency not known	Immune-mediated necrotising myopathy
Reproductive system and breast disorders	Less frequent	Gynaecomastia, impotence
General disorders and administration site conditions	Less frequent	Malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia
Investigations	Frequent	Liver function test abnormal, blood creatine kinase increased
	Less frequent	White blood cells urine positive
Injury, poisoning and procedural complications	Frequency unknown	Accidental injury.

d. Paediatric population
No clinically significant effect on growth and sexual maturation was observed in children.
The safety and tolerability profile in paediatric patients are similar to the known safety profile of atorvastatin in adult patients.
Based on the data available, the frequency, type and severity of adverse reactions in children is similar to adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Overdose
There is no specific treatment available for CHOLMIN overdose. Should an overdose occur, the patient should be treated symptomatically, and supportive measures instituted, as required. Liver function tests should be performed, and serum CK levels should be monitored. Due to extensive binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5 PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
A 7.5 Serum-cholesterol reducers
Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.
The liver is its primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) clearance.
In animal models, atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and increasing the number of LDL-C receptors on the cell surface of liver cells, providing for enhanced uptake and catabolism of LDL-C.
Atorvastatin reduces LDL-C production and the number of LDL-C particles. Depending on dose, atorvastatin reduces the number of apolipoprotein-B-containing particles in patients with hypercholesterolaemia. Atorvastatin produces a profound and sustained increase in LDL-C receptor activity coupled with a beneficial change in the quality of circulating LDL-C particles.
Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicines.
Atorvastatin reduces total cholesterol (total-C), LDL-C, apolipoprotein-B in normal volunteers, and in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia, mixed dyslipidaemia, and in some patients with homozygous familial hypercholesterolaemia. It also reduces serum triglycerides (TG) and produces variable increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A-1 in non-familial hypercholesterolaemia and mixed dyslipidaemias.

Pharmacokinetic properties
Absorption
Atorvastatin is 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. Although food decreases the rate and extent of absorption by approximately 25 % and 9 %, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30 % for C_{max} and AUC) following evening administration compared to morning administration of the medicine. However, LDL-C reduction is the same regardless of the time of medicine administration (see section 4.2).

Distribution
Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥ 98 % or more bound to plasma proteins.

Biotransformation
Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. 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.

Elimination
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, it does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of a dose of atorvastatin is recovered in urine following oral administration.

Special population
Elderly:
Plasma concentrations of atorvastatin and its active metabolites are higher (approximately 40 % for C_{max} and 30 % for AUC) in healthy elderly subjects than in young adults while the lipid effects were comparable to that seen in younger patient populations.
Gender:
Plasma concentrations of atorvastatin in women differ (approximately 20 % higher for Cmax and 10 % lower for AUC) from those in men; however, there is no clinically significant difference in lipid effects among men and women.
Renal insufficiency:
Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary (see section 4.2). However, a history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects (see section 4.4).
Hepatic insufficiency:
Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).
Haemodialysis:
While studies have not been conducted in patients with end-stage renal disease, haemodialysis is not expected to significantly enhance clearance of atorvastatin since the medicine is extensively bound to plasma proteins.

SLCO1B1 polymorphism
Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2,4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

Paediatric population
Oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC are observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Preclinical safety data
Not applicable

6 PHARMACEUTICAL PARTICULARS
List of excipients
Sodium lauryl sulfate
Colloidal anhydrous silica
Anhydrous sodium carbonate
Mannitol
Butylhydroxyanisole
Microcrystalline cellulose
Croscarmellose Sodium
Magnesium stearate
Film-coating
Hypromellose
Microcrystalline cellulose
Stearic acid
Incompatibilities
Not applicable
Shelf life
36 months
Special precautions for storage
Store in the original packaging (in the carton) at or below 25 °C.
Nature and contents of container
Aluminium/Aluminium blister [Aluminium Foil of cold form blister (Lidding foil) and Cold form laminate for Alu Alu blister (Forming foil)] strips (4 blisters of 7 tablets) in a cardboard carton containing 28 film-coated tablets.
Special precautions for disposal and other handling
No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd
106 16th Road
Building 2, Midrand
South Africa

8 REGISTRATION NUMBER(S)
Cholmin 10: 49/7.5/0481
Cholmin 20: 49/7.5/0482
Cholmin 40: 49/7.5/0483
Cholmin 80: 49/7.5/0484

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16 March 2021

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SKEDULERINGSTATUS S4

1 NAAM VAN DIE MEDISYNE
CHOLMIN 10 (film-bedekte tablette)
CHOLMIN 20 (film-bedekte tablette)
CHOLMIN 40 (film-bedekte tablette)
CHOLMIN 80 (film-bedekte tablette)

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
CHOLMIN 10: Elke film-bedekte tablet bevat atorvastatienkalsiumtrihidraat, gelykstaande aan 10 mg atorvastatien. Bevat suiker: 70,97 mg mannitol
CHOLMIN 20: Elke film-bedekte tablet bevat atorvastatienkalsiumtrihidraat, gelykstaande aan 20 mg atorvastatien. Bevat suiker: 141,94 mg mannitol
CHOLMIN 40: Elke film-bedekte tablet bevat atorvastatienkalsiumtrihidraat, gelykstaande aan 40 mg atorvastatien. Bevat suiker: 283,88 mg mannitol
CHOLMIN 80: Elke film-bedekte tablet bevat atorvastatienkalsiumtrihidraat, gelykstaande aan 80 mg atorvastatien. Bevat suiker: 567,76 mg mannitol
Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1

3 FARMASEUTIESE VORM
CHOLMIN 10: Wit gekleurde, ovaalvormige, bikonvekse film-bedekte tablette aan een kant gebosseleer met "10" en plein aan die ander kant.
CHOLMIN 20: Wit gekleurde, ovaalvormige, bikonvekse film-bedekte tablette aan een kant gebosseleer met "20" en plein aan die ander kant.
CHOLMIN 40: Wit gekleurde, ovaalvormige, bikonvekse film-bedekte tablette aan een kant gebosseleer met "40" en plein aan die ander kant.
CHOLMIN 80: Wit gekleurde, ovaalvormige, bikonvekse film-bedekte tablette aan een kant gebosseleer met "80" en plein aan die ander kant.

4 KLINIESE BESONDERHEDE
Terapeutiese indikasies
Hipercholesterolemie
CHOLMIN is aangedui:
- As aanvulling by 'n dieet vir die verlaging van verhoogde totale cholesterol, LDL-cholesterol, apolipoproteïen-B, trigliseriedvlakke en om die HDL-cholesterol matig te verhoog by pasiënte met primêre hipercholesterolemie (oorerflike familiale en nie-familiale hipercholesterolemie) en gekombineerde/gemengde dislipidemie;
- Om totale-C en LDL-C te verlaag by pasiënte met oorerflike familiale hipercholesterolemie as aanvulling tot ander lipied-verlagende behandeling (bv. LDL aferese) of indien die soort behandelings nie beskikbaar is nie.

Pediatriese pasiënte (10 – 17 jaar oud)
CHOLMIN is aangedui as aanvulling by 'n dieet om totale-C, LDL-C en apo-B vlakke in seuns en post-menargale dogters, > 10 tot 17 jaar oud, met oorerflike familiale hipercholesterolemie, wanneer, na 'n voldoende tydperk van dieet-terapie, die volgende uitslae verkry word:
- LDL-C steeds ≥ 4,98 mmol/L (190 mg/dL) bly of
- LDL-C steeds ≥ 4,04 mmol/L (160 mg/dL) bly en:
- Daar 'n positiewe familiegeskiedenis van premature kardiovaskulêre siekte (KVS) is of,
- Twee of meer ander KVS risikofaktore by die pediatriese pasiënt aangetref word.

Vermindering van kardiovaskulêre komplikasies
By pasiënte sonder klinies duidelike kardiovaskulêre siektes, met of sonder dislipidemie, maar met veelvuldige risikofaktore vir koronêre hartsiektes soos rook, hipertensie, diabetes, lae HDL-C, of 'n familiegeskiedenis van vroeë koronêre hartsiektes, word CHOLMIN aangedui om die risiko van iskemiese kardiovaskulêre en serebrovaskulêre siektes te verminder.
Sekondêre voorkoming
Vermindering van kardiovaskulêre insidente by pasiënte met duidelike kliniese koronêre hartsiekte en verhoogde cholesterolvlakke.
Terapie met lipied-verlagende middels moet 'n deel uitmaak van veelvuldige risiko-faktor-ingryping in persone wat aan 'n verhoogde risiko van aterosklerotiese vaskulêre siekte, as gevolg van hipercholesterolemie, blootgestel is. Lipied-verandering middels moet saam met 'n dieet wat beperk is ten opsigte van versadigde vet en cholesterol, gebruik word, alleenlik wanneer die resultate van dieet en ander nie-farmakologiese ingrepe onvoldoende is.
Alvorens CHOLMIN-terapie begin word, moet sekondêre oorsake van hipercholesterolemie (bv. swak beheerde diabetes mellitus, hipotiroïdisme, nefrotiese sindroom, disproteïnemie, obstruktiewe lewersiekte, ander geneesmiddelbehandeling en alkoholisme), uitgeskakel word, en 'n lipiedprofiel moet uitgevoer word om totale-C, LDL-C, HDL-C en TG te bepaal.

Posologie en metode van toediening
Die pasiënt moet op 'n standaard cholesterol-verlagende dieet geplaas word alvorens hy/sy CHOLMIN ontvang en moet voort gaan met die dieet tydens CHOLMIN-behandeling.
Die gebruiklike aanvangsdosis is 10 mg een keer per dag en moet op 'n individuele basis bereken word volgens basislyn LDL-C vlakke, die doel van die terapie en respons van die pasiënt. Dosisaanpassings moet slegs na 4 weke of langer gemaak word. Die maksimum aanbevole dosis sal afhang van die indikasie (sien hieronder).

Primêre hipercholesterolemie en gemengde hipercholesterolemie:
Die meerderheid pasiënte kan met 10 mg CHOLMIN een keer per dag beheer word. 'n Terapeutiese respons word binne 2 weke duidelik, en maksimum respons word gewoonlik binne 4 weke verkry. Die response word tydens kroniese terapie onderhou.

Heterosigotiese familiale hipercholesterolemie in pediatriese pasiënte (> 10 – 17 jarige ouderdom)
Ervaring in pediatriese pasiënte is beperk tot 'n klein aantal pasiënte (ouderdomsgroep 10 – 17 jaar) met erge dislipidemie, soos familiale hipercholesterolemie.
Pasiënte moet met CHOLMIN 10 mg daagliks begin word, die maksimum aanbevole dosis is 20 mg/dag.

Homosigotiese familiale hipercholesterolemie
In 'n uitgebreide gebruik en onbeheerde studie van pasiënte met homosigotiese familiale hipercholesterolemie, het die meerderheid pasiënte op 'n dosis van 80 mg CHOLMIN gereageer, met 'n groter as 15 % verlaging in LDL-C (18 % tot 45 %).

Vermindering van kardiovaskulêre komplikasies
Die dosisreikwydte is 10 tot 80 mg daagliks.

Spesiale pasiëntgroepe
Dosering in pasiënte met renale inkorting:
Renale siekte het geen invloed op plasmakonsentrasies of lipiedeffekte van CHOLMIN nie. Geen dosisaanpassings is dus nodig nie (sien afdeling 4.4).

Dosering in pasiënte met hepatiese inkorting:
In persone wat matige tot ernstige hepatiese inkorting, bly die terapeutiese respons teenoor CHOLMIN onveranderd, maar serumvlakke van die geneesmiddel word aansienlik verhoog. In pasiënte met kroniese alkoholiese lewersiekte, is plasmakonsentrasies van atorvastatien aansienlik verhoog. K_{maks} en AOK is albei 4 keer hoër in pasiënte met Child-Pugh A siekte. K_{maks} en AOK is onderskeidelik ongeveer 16 en 11 keer hoër in pasiënte met Child-Pugh B siekte. Die doserings vir pasiënte wat aansienlike volumes alkohol inneem en/of 'n geskiedenis van lewersiekte het moet versigtig oorweeg word (sien afdeling 4.3 en 4.4).

Metode van toediening
CHOLMIN is vir orale toediening.
Dosisse kan ter enige tyd van die dag, met of sonder kos gegee word.

Kontraïndikasies
CHOLMIN is teenaangedui in pasiënte:
- met hipersensitiwiteit teenoor atorvastatien of enige van die ander hulpstowwe van CHOLMIN soos gelys in afdeling 6.1.
- met aktiewe lewersiekte of onverklaarbare aanhoudende verhogings in serumtransaminase wat die boonste limiet van normaal drie keer oortref.
- wat swanger is, tydens borsvoeding en vroue wat potensieel vrugbaar is en nie voldoende voorbehoeding toepas nie (sien afdeling 4.6).
- wat behandel word met die hepatitis C antivirale middels glecaprevir/pibrentasvir.
- wat met rifampisien of diltiasiem behandel word en pomelo sap drink (sien afdeling 4.5).
- met Child-Pugh B en C (lewersirrose).

Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Lewereffekte
Dit word aanbeveel dat lewerfunksietoetse voor begin van terapie en met gereelde tussenposes daarna, uitgevoer word. Pasiënte wat tekens en simptome van lewerskade ontwikkel, se lewerfunksietoetse moet gedoen word. Pasiënte wat verhoogde transaminasevlakke ontwikkel, moet gemonitor word totdat die abnormaliteit(e) verdwyn. Indien 'n verhoging in transaminase van meer as 3 keer die boonste grenswaarde van normaal (BGN) aanhou, word onttrekking van CHOLMIN aanbeveel (sien afdeling 4.8).
CHOLMIN moet met omsigtigheid gebruik word in pasiënte wat aansienlike volumes alkohol inneem en/of 'n geskiedenis van lewersiekte het.

Voorbehoeding van beroerte by Aggressiewe Vermindering in Cholesterol-vlakke (SPARCL)
In 'n post-hoc analise van beroerte-subtipes by pasiënte sonder koronêre hartsiekte (KHS) wat 'n beroerte of kortstondige iskemiese aanval (TIA) gehad het, was daar 'n hoër voorkoms van hemorragiese beroerte by pasiënte wat op atorvastatien 80 mg begin is in vergelyking met placebo. Die verhoogde risiko is veral opgemerk by pasiënte met voorafgaande hemorragiese beroerte of lakunêre infarksie tydens die inskrywing van die studie. Vir pasiënte met 'n voorafgaande bloeding of lakunêre infarksie, is die balans tussen die risiko's en voordele van CHOLMIN 80 mg onseker, en die moontlike risiko van hemorragiese beroerte moet noukeurig oorweeg word voordat die behandeling begin word (sien afdeling 5.1).

Skeletspier effekte
Atorvastatien kan die skeletspier beïnvloed en mialgie, miositis en miopatie veroorsaak wat kan lei tot rabdomiolise, 'n potensieel lewensgevaarlike toestand wat gekenmerk word deur merkbaar verhoogde kreatienfosfokinase (KFK) vlakke (> 10 keer BGN), mioglobinemie en mioglobinurie wat kan lei tot nierversaking.
Daar was baie min verslae van 'n immuun-gemedieerde nekrotiserende miopatie (IGNM) tydens of na behandeling met sommige statiene. IGNM word klinies gekenmerk deur aanhoudende proksimale spierswakheid en verhoogde serum kreatienfosfokinase, wat voortduur ondanks die staking van statienbehandeling.

Voor die behandeling
Atorvastatien moet met omsigtigheid voorgeskryf word by pasiënte met voor-onthullende faktore vir rabdomiolise. KFK-vlakke moet gemeet word voordat statienbehandeling in die volgende situasies begin mag word:
- Renale inkorting
- Hipotireose
- Persoonlike of familiale geskiedenis van oorerflike spierafwykings
- Vorige geskiedenis van spiertoksisiteit met 'n statien of fibraat
- Vorige geskiedenis van lewersiekte en / of waar aansienlike hoeveelhede alkohol verbruik word
- By bejaardes (ouderdom > 70 jaar) moet die noodsaaklikheid van sodanige meting oorweeg word, volgens die teenwoordigheid van ander predisponerende faktore vir rabdomiolise
- Situasies waar 'n toename in plasmavlakke kan voorkom, soos interaksies (sien afdeling 4.5) en spesiale bevolkingsgroepe, insluitend genetiese subpopulasies (sien afdeling 5.2)

In sulke situasies moet die risiko van behandeling oorweeg word met betrekking tot moontlike voordele, en kliniese waarneming word aanbeveel. As KFK-vlakke beduidend verhoog is (> 5 keer BGN) aan die beginpunt, moet die behandeling nie begin word nie.
Meting van KFK
KFK moet nie gemeet word na inspannende oefening of in die teenwoordigheid van enige geloofwaardige alternatiewe oorsake van toename in KFK nie, aangesien dit waardeinterpretasie bemoeilik. As KFK-vlakke beduidend verhoog is by die basislyn (> 5 keer BGN), moet die vlakke binne 5 tot 7 dae later herwaardeer word om die resultate te bevestig.
Tydens behandeling
- Pasiënte moet gevra word om spierpyn, krampe of swakheid onmiddellik aan te meld, veral as dit gepaard gaan met malaise of koors.
- As sulke simptome voorkom terwyl 'n pasiënt behandeling met CHOLMIN ontvang, moet hul KFK-vlakke gemeet word. As daar gevind word dat hierdie vlakke beduidend verhoog is (> 5 keer BGN), moet die behandeling gestaak word.
- As spier-simptome ernstig is en daaglikse ongemak veroorsaak, selfs al word die KFK-vlakke tot ≤ 5 x BGN verhoog, moet die staking van die behandeling oorweeg word.
- As simptome verdwyn en die KFK-vlakke na normaal terugkeer, kan die herinvoering van atorvastatien of die instelling van 'n alternatiewe statien met die laagste dosis en met noukeurige waarneming, oorweeg word.
- CHOLMIN moet gestaak word indien klinies beduidende verhoging van KFK-vlakke (> 10 x BGN) voorkom, of as rabdomiolise gediagnoseer of vermoed word.

Gelyktydige behandeling met ander medisyne
Die risiko van rabdomiolise word verhoog wanneer atorvastatien gelyktydig toegedien word met sekere medisyne wat die plasmakonsentrasie van atorvastatien kan verhoog, soos kolgisien, kragtige inhibeerders van CYP3A4 of vervoerproteïene (bv. siklosporien, telitromisien, klaritromisien, delavirdien, stiripentol, ketokonasool, vorikonasool, itrakonasool, posakonasool, letemovir en MIV-protease-inhibeerders, insluitend atasanavir, indinavir, sakinavir met ritonavir, lopinavir met ritonavir, tipranavir met ritonavir, darunavir met ritonavir, fosamprenavir en fosamprenavir met ritonavir en sitochroom P450 inhibeerders). Die risiko van miopatie kan ook verhoog word met die gelyktydige gebruik van gemfibrosiel en ander veselsuurderivate, antivirale middels vir die behandeling van hepatitis C (HCV) (boseprevir, televir, elbasvir / grasoprevir), eritromisien, niasien of ezetimibe. Indien moontlik, moet alternatiewe (nie-interaksie) terapie oorweeg word in plaas van hierdie medisyne.
In gevalle waar gelyktydige toediening van hierdie medisyne met CHOLMIN nodig is, moet die voordeel en die risiko van gelyktydige behandeling noukeurig oorweeg word. As pasiënte medisyne ontvang wat die plasmakonsentrasie van atorvastatien verhoog, word 'n laer maksimum dosis atorvastatien aanbeveel. Daarbenewens, in die geval van kragtige CYP3A4-inhibeerders, moet 'n laer aanvangsdosis CHOLMIN oorweeg word en toepaslike kliniese waarneming van hierdie pasiënte word aanbeveel (sien afdeling 4.5).

CHOLMIN moet nie saam met sistemiese formulerings van fusidiensuur toegedien word, of binne 7 dae na die behandeling met fusidiensuur nie. By pasiënte waar die gebruik van sistemiese fusidiensuur as noodsaaklik beskou word, moet statienbehandeling gestaak word gedurende die duur van die behandeling met fusidiensuur. Daar is al berig oor rabdomiolise (insluitend sommige sterftes) by pasiënte wat fusidiensuur en statiene in kombinasie ontvang (sien afdeling 4.5). Die pasiënt moet aangeraai word om onmiddellik mediese hulp in te win indien simptome van spierswakheid, pyn of teerheid ervaar word. Statienterapie kan sewe dae na die laaste dosis fusidiensuur weer ingestel word. In buitengewone omstandighede, waar langdurige sistemiese fusidiensuur nodig is byvoorbeeld, vir die behandeling van ernstige infeksies, moet die behoefte aan gelyktydige toediening van CHOLMIN en fusidiensuur slegs van geval tot geval, en onder noukeurige mediese toesig, oorweeg word.
CHOLMIN-terapie moet onttrek word by enige pasiënt met 'n akute, ernstige toestand wat dui op 'n miopatie of wat 'n risikofaktor het wat geneig is tot die ontwikkeling van nierversaking sekondêr tot rabdomiolise, (bv. ernstige akute infeksie, hipotensie, groot chirurgie, trauma, ernstige metaboliese-, endokriene- en elektrolietafwykings, en onbeheerde epileptiese aanvalle).

Interstisiële longsiekte
Uitsonderlike gevalle van interstisiële longsiekte is by sommige statiene aangemeld, veral met langtermynterapie (sien afdeling 4.8). Kenmerkende dispnee, nie-produktiewe hoes en agteruitgang in algemene gesondheid (moegheid, gewigsverlies en koors) kan ingesluit word. As vermoed word dat 'n pasiënt interstisiële longsiekte ontwikkel het, moet statienterapie gestaak word.

Diabetes Mellitus
Stygings in HbA1c en vastende serumglukose-vlakke is by HMG-KoA reduktase-inhibeerders, insluitend CHOLMIN, gerapporteer.
Sommige bewyse dui daarop dat statiene as 'n klas, bloedglukose verhoog en by sommige pasiënte, met 'n hoë risiko vir toekomstige diabetes, 'n vlak van hiperglisemie kan veroorsaak waar formele diabetesversorging toepaslik is. Hierdie risiko word egter opgeweeg deur die vermindering in vaskulêre risiko by statiene en behoort daarom nie 'n rede te wees om die behandeling van statien te staak nie. Pasiënte wat in gevaar is (vastende glukose 5,6 tot 6,9 mmol/L, BMI > 30 kg/m^2, verhoogde trigliseriede, hipertensie) moet klinies en biochemies gemonitor word volgens nasionale riglyne.

Pediatriese pasiëntgroepe
Geen klinies beduidende effek op groei en seksuele rypwording is waargeneem in 'n drie-jaar studie nie, gebaseer op die beoordeling van algehele rypwording en ontwikkeling, assessering van Tanner-vase en meting van lengte en gewig (sien afdeling 4.8).

Interaksie met ander medisyne en ander vorms van interaksie
Effek van gelyktydige toegediende medisyne op atorvastatien
Atorvastatien word gemetaboliseer deur sitochroom P450 3A4 (CYP3A4) en is 'n substraat van die hepatiese vervoerders, organiese anioon polipeptied 1B1 (OATP1B1) vervoerder en 1B3 (OATP1B3) vervoerder. Metaboliete van atorvastatien is substrate van OATP1B1. Atorvastatien word ook geïdentifiseer as 'n substraat van die multi-geneesmiddelweerstandige proteïen 1 (MGW1) en borskankerweerstandige proteïen (BKWP), wat die dermabsorpsie en galopruiming van atorvastatien kan beperk (sien afdeling 5.2). Gelyktydige toediening van medisyne wat CYP3A4-inhibeerders of vervoerproteïene is, kan lei tot verhoogde plasmakonsentrasies van atorvastatien en 'n verhoogde risiko vir miopatie. Die risiko kan ook verhoog word by gelyktydige toediening van atorvastatien met ander medisyne wat die potensiaal het om miopatie te veroorsaak, soos veselsuurderivate en ezetimibe (sien afdeling 4.4).

CYP3A4 inhibeerders
Daar is getoon dat kragtige CYP3A4-inhibeerders tot 'n beduidende toename in konsentrasies atorvastatien lei. Gelyktydige toediening van kragtige CYP3A4-inhibeerders (bv. siklosporien, telitromisien, klaritromisien, delavirdien, stiripentol, ketokonasool, vorikonasool, itrakonasool, posakonasool, sommige antivirale middels wat gebruik word in die behandeling van HCV (bv. elbasvir / grazoprevir) en MIV-protease-inhibeerders, insluitend ritonavir, lopinavir, atazanavir, indinavir, darunavir), moet indien moontlik vermy word. In gevalle waar gelyktydige toediening van hierdie medisyne met CHOLMIN nie vermy kan word nie, moet laer aanvangs- en maksimum dosisse CHOLMIN oorweeg word en toepaslike kliniese waarneming van die pasiënt word aanbeveel.
Matige CYP3A4-inhibeerders (bv. eritromisien, diltiasiem, verapamil en flukonasool) kan die plasmakonsentrasies van atorvastatien verhoog. 'n Verhoogde risiko van miopatie is waargeneem met die gebruik van eritromisien in kombinasie met statiene. Dit is bekend dat beide amiodaron en verapamil CYP3A4-aktiwiteit belemmer, en saam met toediening met atorvastatien kan dit lei tot verhoogde blootstelling aan atorvastatien. Daarom moet 'n laer maksimum dosis CHOLMIN oorweeg word en toepaslike kliniese monitering van die pasiënt word aanbeveel wanneer dit saam met matige CYP3A4-inhibeerders gebruik word. Toepaslike kliniese waarneming word aanbeveel na aanvang of na die dosisaanpassings van die inhibeerder.

CYP3A4 induseerders
Gelyktydige toediening van CHOLMIN met induseerders van sitochroom P450 3A (bv. efavirens, rifampien, Sint-Janskruid) kan lei tot wisselende verlaging in plasmakonsentrasies van atorvastatien. As gevolg van die tweeledige meganisme van rifampien, (sitochroom P450 3A induksie en inhibering van die opname van die hepatosiet OATP1B1) word gelyktydige toediening van CHOLMIN en rifampien nie aanbeveel nie, aangesien vertraagde toediening van atorvastatien soos in CHOLMIN na toediening van rifampisien geassosieer is met 'n beduidende verlaging in die plasmakonsentrasies van atorvastatien. Die effek van rifampisien op atorvastatien konsentrasies in hepatosiete is egter onbekend en as gelyktydige toediening nie vermy kan word nie, moet pasiënte noukeurig gemonitor word vir effektiwiteit.

Vervoerinhibeerders
Inhibeerders van vervoerproteïene (bv. siklosporien, letermovir) kan die sistemiese blootstelling van atorvastatien verhoog. Die effek van die hepatiese opname vervoerders inhibisie op atorvastatien konsentrasies in hepatosiete is onbekend. As gelyktydige toediening nie vermy kan word nie, word 'n vermindering in dosis en kliniese monitering vir effektiwiteit aanbeveel. Die gebruik van CHOLMIN word nie aanbeveel by pasiënte wat letermovir saam met siklosporien neem nie (sien afdeling 4.4).

Gemfibrosiel / veselsuurderivate
Die gebruik van fibrate alleen word soms geassosieer met spierverwante reaksies, insluitend rabdomiolise. Die risiko vir hierdie gebeure kan verhoog word met die gepaardgaande gebruik van veselsuurderivate en atorvastatien. As gelyktydige toediening nie vermy kan word nie, moet die laagste dosis atorvastatien om die terapeutiese doelwit te bereik, gebruik word en die pasiënte moet toepaslik gemonitor word (sien afdeling 4.4).

Ezetimibe
Die gebruik van ezetimibe alleen hou verband met spierverwante gebeure, insluitend rabdomiolise. Die risiko vir hierdie gebeure kan dus verhoog word met die gelyktydige gebruik van ezetimibe en atorvastatien. Toepaslike kliniese waarneming van hierdie pasiënte word aanbeveel.

Kolestipol
Plasmakonsentrasies van atorvastatien en die aktiewe metaboliete daarvan was laer (met ongeveer 25 %) toe kolestipol saam met atorvastatien toegedien is. Lipiede-effekte was egter groter toe atorvastatien en kolestipol saam toegedien is
as wanneer een van die medisyne alleen toegedien is.

Fusidiensuur
Die risiko van miopatie, insluitend rabdomiolise, kan verhoog word deur die gelyktydige toediening van sistemiese fusidiensuur met statiene. Die meganisme van hierdie interaksie (of dit farmakodinamiese of farmakokinetiese is, of albei) is nog onbekend. Daar is al berig oor rabdomiolise (insluitend sommige sterftes) by pasiënte wat hierdie kombinasie ontvang.
As behandeling met sistemiese fusidiensuur nodig is, moet die behandeling met CHOLMIN gestaak word gedurende die duur van die behandeling met fusidiensuur (sien afdeling 4.4).

Kolgisien
Alhoewel interaksiestudies met atorvastatien en kolgisien nie uitgevoer is nie, is gevalle van miopatie gerapporteer met atorvastatien wat saam met kolgisien toegedien is, en dus moet CHOLMIN met sorg voorgeskryf word saam met kolgisien.

Teensure
Gelyktydige toediening van 'n orale teensuurmiddel-suspensies wat magnesium en aluminiumhidroksiede bevat, kan die plasmakonsentrasies van atorvastatien verlaag, maar LDL-C-verlaging sal egter nie verander word nie.

Effek van atorvastatien op gelyktydige toegediende medisyne
Digoksien
Gelyktydige toediening van veelvuldige dosisse atorvastatien en digoksien het gelykvlak plasma-digoksienkonsentrasies effens verhoog. Pasiënte wat digoksien neem, moet toepaslik gemonitor word.

Orale voorbehoedmiddels
Gelyktydige toediening van atorvastatien en 'n orale voorbehoedmiddel het die plasmakonsentrasies van noretindroon en etinielestradiol verhoog.

Warfarien
In 'n kliniese studie by pasiënte wat kroniese warfarien-terapie ontvang het, het die daagliks toediening van atorvastatien met warfarien 'n klein afname in protrombientyd veroorsaak gedurende die eerste 4 dae van dosering, wat binne 15 dae na atorvastatien-behandeling weer teruggekeer het na normaal. Alhoewel slegs baie seldsame gevalle van klinies beduidende antikoagulant-interaksies aangemeld is, moet protrombientyd bepaal word voordat atorvastatien begin word by pasiënte wat warfarien neem en gereeld genoeg tydens vroeë terapie om te verseker dat geen noemenswaardige verandering van protrombientyd plaasvind nie. Sodra 'n stabiele protrombientyd gedokumenteer is, kan protrombientye gemonitor word met die tussenposes wat gewoonlik aanbeveel word vir pasiënte op warfarien. Indien die dosis van atorvastatien verander of gestaak word, moet dieselfde prosedure herhaal word. Atorvastatien-terapie word nie geassosieer met bloeding of veranderinge in protrombientyd by pasiënte wat nie antikoagulante gebruik nie.

Pediatriese pasiëntgroepe
Interaksiestudies is slegs by volwassenes uitgevoer. Die omvang van interaksies in die pediatriese populasie is onbekend. Bogenoemde interaksies vir volwassenes en die waarskuwings in afdeling 4.4 moet in ag geneem word vir die pediatriese populasie.

Pomelosap
Pomelosap bevat een of meer komponente wat CYP 3A4 inhibeer en die plasmakonsentrasies van CHOLMIN met 2,5 tot 3,3 maal kan verhoog. Daarom moet die kombinasie vermy word (sien afdeling 4.3).

Vrugbaarheid, swangerskap en borsvoeding
Potensieel vrugbare vrouens
Vrouens wat potensieel vrugbaar is moet voldoende voorbehoedende maatreëls toepas tydens behandeling (sien afdeling 4.3).

Swangerskap
CHOLMIN is teenaangedui tydens swangerskap (sien afdeling 4.3). Veiligheid by swanger vroue is nie vasgestel nie. Behandeling tydens swangerskap met CHOLMIN kan die fetale vlakke van mevalonaat, wat 'n voorloper van biosintese van cholesterol is, verminder. Aterosklerose is 'n kroniese proses, en die staking van lipied-verlagende medisyne tydens swangerskap behoort gewoonlik 'n klein impak te hê op die langtermynrisiko verbonde aan primêre hipercholesterolemie. Om hierdie redes moet CHOLMIN nie gebruik word by vroue wat swanger is, probeer swanger raak of vermoed dat hulle swanger is nie. Behandeling met CHOLMIN moet gestaak word vir die duur van die swangerskap of totdat daar vasgestel is dat die vrou nie swanger is nie (sien afdeling 4.3.).

Laktasie
Dit is nie bekend of atorvastatien of die metaboliete daarvan in menslike melk uitgeskei word nie. By rotte is die plasmakonsentrasies van atorvastatien en die aktiewe metaboliete daarvan soortgelyk aan dié in melk. Vanweë die potensiaal vir ernstige nadelige reaksies, moet vroue wat CHOLMIN inneem nie hul babas borsvoed nie (sien afdeling 4.3). Dus is CHOLMIN teenaangedui tydens borsvoeding (sien afdeling 4.3).

Vrugbaarheid
In dierestudies het atorvastatien geen invloed op manlike of vroulike vrugbaarheid gehad nie.

Uitwerking op die vermoë om te bestuur en masjiene te gebruik
CHOLMIN het 'n weglaatbare invloed op die vermoë om te bestuur of om masjinerie te hanteer.

Newe-effekte
b. Getabuleerde opsomming van newe-effekte

MedDRA Sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Infeksies en infestasies	Gereeld	Infeksie, griepsindroom, Nasofaringitis
Bloed- en limfatiesestelsel afwykings	Minder gereeld	Trombositopenie
Immuunstelsel afwykings	Gereeld	Allergiese reaksies
	Minder gereeld	Anafilakse
Metabolisme- en voeding afwykings	Gereeld	Hiperglisemie
	Minder gereeld	Hipoglisemie, gewigstoename, anoreksie
Psigiatriese afwykings	Minder gereeld	Nagmerries, slaaploosheid
Senuweestelsel afwykings	Gereeld	Hoofpyn
	Minder gereeld	Duiseligheid, parestesie, hipoëstesie, disgeusie, amnesie, perifere neuropatie
Oog versteurings	Minder gereeld	Dowwe visie, visie steurnisse
Versteurings van die ore en labirint	Minder gereeld	Tinnitus, gehoor verlies
Respiratoriese-, torakale- en mediastinale versteurings	Gereeld	Sinusitis, faringitis, faringeale- en laringeale pyn, epistakse
Gastro-intestinale versteurings	Gereeld	Hardlywigheid, winderigheid, dispepsie, naarheid, diarree
	Minder gereeld	Braking, boonste en onderste buikpyn, eruktasie, pankreatitis
Hepatobiliêre versteurings	Minder gereeld	Hepatitis, cholestase, lewerversaking
Versteurings van die vel en subkutane weefsel	Minder gereeld	Urtikaria, veluitslag, pruritus, alopesie, angioneurotiese edeem, bulleuse dermatitis insluitend eritem multiforme, Stevens-Johnson sindroom en toksiese epidermale nekrolise
Skeletspier en bindweefsel afwykings	Gereeld	Mialgie, artralgie, pyn in ekstremiteite, spierkrampe, gewrig swelling, rugpyn
	Minder gereeld	Nekpyn, spieruitputting, miopatie, miositis, rabdomiolise, spier skeuring, tendonopatie, soms bemoeilik deur skeuring, lupus-agtige sindroom.
	Frekwensie onbekend	Immuun-gemedieerde nekrotiserende miopatie
Voortplantingsisteem- en borsversteurings	Minder gereeld	Ginekomastie, impotensie
Algemene versteurings en toestande by die toedieningsplek	Minder gereeld	Malaise, astenie, borspyn, perifere edeem, moegheid, pireksie
Ondersoeke	Gereeld	Abnormale lewerfunksie toets, bloed KFK toename
	Minder gereeld	Urien-positiewe witbloedselle
Beserings, vergiftiging en prosedurele komplikasies	Frekwensie onbekend	Toevallige besering

d. Pediatriese pasiëntgroepe
Geen klinies beduidende effek op groei en seksuele rypwording is by kinders waargeneem nie.
Die veiligheid- en verdraagsaamheidsprofiel by pediatriese pasiënte is soortgelyk aan die bekende veiligheidsprofiel van atorvastatien by volwassenes.
Op grond van die beskikbare data is die frekwensie, tipe en erns van nadelige reaksies by kinders soortgelyk aan volwassenes.

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedkeur is, te rapporteer. Dit laat volgehoue kontrolering van voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "**6.04 Adverse Drug Reaction Reporting Form**", aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/Publications/Index/8

Oordosering
Daar is geen spesifieke behandeling beskikbaar vir CHOLMIN oordosering nie. Indien oordosering plaasvind, moet die pasiënt simptomaties behandel word en ondersteunende maatreëls soos nodig ingestel word. Lewerfunksietoetse moet uitgevoer word en serum KFK-vlakke moet gemonitor word. As gevolg van die uitgebreide binding van die geneesmiddel aan plasmaproteïene, word verwag dat hemodialise nie die opruiming van atorvastatien aansienlik sal verhoog nie.

5 FARMAKOLOGIESE EIENSKAPPE
Farmakodinamiese eienskappe
A 7.5 Anti-serumcholesterolmiddels
Farmakoterapeutiese groep: Lipied wysigende middels, HMG-KoA-reduktase inhibeerders, ATC kode: C10AA05

Atorvastatien is 'n selektiewe, kompeterende inhibeerder van HMG-KoA-reduktase, wat die spoedbeperkende ensiem is wat verantwoordelik is vir die omskakeling van 3-hidroksi-3-metiel-glutariel-koënsiem-A na mevalonaat, 'n voorloper van sterole, insluitend cholesterol.
Die lewer is die primêre setel van aksie en die hoofsetel van cholesterolsintese en lae-densiteit lipoproteïene cholesterol (LDL-C) opruiming.
In dieremodelle verlaag atorvastatien plasma cholesterol- en lipoproteïen-serumkonsentrasies deur HMG-KoA-reduktase en cholesterolsintese in die lewer te inhibeer en die aantal LDL-C-reseptore op die selopperVlak van lewerselle te verhoog, wat voorsiening maak vir verhoogde opname en katabolisme van LDL- C.
Atorvastatien verminder LDL-C-produksie, asook die aantal LDL-C-partikels. Afhangend van die dosis, sal atorvastatien die aantal apolipoproteïne-B-bevattende partikels in pasiënte met hipercholesterolemie verminder. Atorvastatien lewer 'n diepgaande en volgehoue toename in LDL-C-reseptoraktiwiteit tesame met 'n gunstige verandering in die kwaliteit van sirkulerende LDL-C-partikels.
Atorvastatien is effektief in die vermindering van LDL-C in pasiënte met homosigotiese familiale hipercholesterolemie, 'n bevolking wat gewoonlik nie op lipiedverlagende medisyne gereageer het nie.
Atorvastatien verminder die totale cholesterol (totaal-C), LDL-C, apolipoproteïen-B in normale vrywilligers, en by pasiënte met heterosigotiese familiale hipercholesterolemie, nie-familiale hipercholesterolemie, gemengde dislipidemie, en by sommige pasiënte met homosigotiese familiale hipercholesterolemie. Dit verminder ook serumtrigliseriede (TG) en veroorsaak wisselende toenames in hoë-densiteit lipoproteïen-cholesterol (HDL-C) en apolipoproteïen-A-1 in nie-familiale hipercholesterolemie en gemengde dislipidemieë.

Farmakokinetiese eienskappe
Absorpsie
Atorvastatien word geabsorbeer na orale toediening, die maksimum plasmakonsentrasies word binne 1 tot 2 uur bereik. Die omvang van die absorpsie neem toe in verhouding tot die dosis van atorvastatien. Die absolute biobeskikbaarheid van atorvastatien is ongeveer 12 % en die sistemiese beskikbaarheid van HMG-KoA-reduktase-inhiberende aktiwiteit is ongeveer 30 %. Die lae sistemiese beskikbaarheid word toegeskryf aan pre-sistemiese opruiming in die gastro-intestinale slymvliese en / of hepatiese eerste-verbygangs-metabolisme. Alhoewel voedsel die spoed en omvang van die opname met onderskeidelik ongeveer 25 % en 9 % verlaag, soos bepaal deur K_{maks} en AOK, is LDL-C-verlaging soortgelyk wanneer atorvastatien met of sonder voedsel gegee word. Die konsentrasie van atorvastatien in plasma is laer (ongeveer 30 % vir K_{maks} en AOK) na toediening in die aand in vergelyking met toediening in die oggend. LDL-C-verlaging is egter dieselfde, afgesien van wanneer die geneesmiddel toegedien word (sien afdeling 4.2).

Verspreiding
Die gemiddelde volume van distribusie vir atorvastatien is ongeveer 381 liter. Atorvastatien word ≥ 98 % of meer gebind aan plasmaproteïene.

Biotransformasie
Atorvastatien word deur sitochroom P450 3A4 gemetaboliseer tot orto- en para-gehidroksileerde derivate en verskeie beta-oksidasie produkte. Afgesien van ander metaboliese weë, word hierdie produkte verder gemetaboliseer via glukuronidase. *In vitro*-inhibisie van HMG-KoA-reduktase deur orto- en para-gehidroksileerde metaboliete is gelykstaande aan dié van atorvastatien. Ongeveer 70 % van die sirkulerende inhiberende aktiwiteit vir HMG-KoA-reduktase word aan aktiewe metaboliete toegeskryf.

Eliminasie
Na hepatiese en/of ekstrahepatiese metabolisme, word atorvastatien hoofsaaklik in die gal uitgeskei. Dit wil voorkom of dit egter nie enterohepatiese hersirkulasie ondergaan nie. Die gemiddelde plasma-eliminasie half-leeftyd van atorvastatien in mense is ongeveer 14 uur, maar die half-leeftyd vir HMG-KoA-reduktase is 20 tot 30 uur as gevolg van die bydrae van aktiewe metaboliete. Minder as 2 % van die dosis atorvastatien word na orale toediening in die urine herwin.

Spesiale pasiëntgroepe
Bejaarde pasiënte:
Plasmakonsentrasies van atorvastatien en sy aktiewe metaboliete is hoër (omtrent 40 % vir K_{maks} en 30 % vir AOK) in gesonde bejaardes in vergelyking met jong volwassenes terwyl die lipiedeffekte vergelykbaar was met dié wat by jonger pasiëntpopulasies gesien is.
Geslag:
Plasmakonsentrasies van atorvastatien by vroue verskil (ongeveer 20 % hoër vir K_{maks} en 10 % laer vir AOK) van dié van mans. Daar is egter geen klinies beduidende verskil in lipied-effekte tussen mans en vrouens nie.
Renale inkorting:
Niersiekte het geen invloed op die plasmakonsentrasies van lipiede-effekte van atorvastatien nie. Dosisaanpassing in pasiënte met renale disfunksie is dus nie nodig nie (sien afdeling 4.2). 'n Geskiedenis van renale inkorting kan egter 'n risikofaktor wees vir die ontwikkeling van rabdomiolise. Hierdie pasiënte vereis nouer waarneming vir skeletspier-effekte (sien afdeling 4.4).
Hepatiese inkorting:
Plasmakonsentrasies van atorvastatien en die aktiewe metaboliete daarvan word aansienlik verhoog (ongeveer 16-voudig vir K_{maks} en 11-voudig vir AOK) by pasiënte met kroniese alkoholiese lewersiekte (Child-Pugh B).
Hemodialise:
Alhoewel studies in pasiënte met eind-stadium niersiekte nie uitgevoer is nie, word daar nie verwag dat hemodialise die opruiming van atorvastatien beduidend sal verhoog nie aangesien die geneesmiddel ekstensief aan plasmaproteïene gebind is.

SLCO1B1 polimorfisme
Hepatiese opname van alle HMG-KoA-reduktase-inhibeerders, insluitend atorvastatien, behels die OATP1B1-vervoerder. In pasiënte met SLCO1B1-polimorfisme is daar 'n bestaande risiko van verhoogde blootstelling aan atorvastatien, wat kan lei tot 'n verhoogde risiko vir rabdomiolise (sien afdeling 4.4). Polimorfisme in die geen kodering OATP1B1 (SLCO1B1 c.521CC) is geassosieer met 'n 2,4-voudige hoër atorvastatien blootstelling (AOK) as by individue sonder hierdie genotipe-variant (c.521TT). 'n Geneties-verswakte hepatiese opname van atorvastatien is ook moontlik by hierdie pasiënte. Dit is nie bekend wat die moontlike gevolge op effektiwiteit is nie.

Pediatriese pasiëntgroepe
Orale opruiming van atorvastatien by pediatriese proefpersone is soortgelyk as in volwassenes wanneer dit allometries volgens liggaamsgewig afgeskaal word. Konsekwente afname in LDL-C en TC word waargeneem oor die reeks atorvastatien en o-hidroksi-atorvastatien blootstelling.

Pre-kliniese veiligheidsdata
Nie van toepassing nie.

6 FARMASEUTIESE BESONDERHEDE
Lys van hulpstowwe
Anhidriese natriumkarbonaat
Butielhidroksianisool
Kolloïdale anhidriese silika
Magnesiumstearaat
Mannitol
Mikrokristallyn sellulose
Natriumkroskarmellose
Natriumlaurielsulfaat
Filmbedekking
Hipromellose
Mikrokristallien sellulose
Steariensuur
Onverenigbaarheid
Nie van toepassing nie.
Rakleeftyd
36 maande.
Spesiale voorsorgmaatreëls tydens berging
Bewaar in die oorspronklike verpakking (in die karton) teen of benede 25 °C.
Aard en inhoud van die houer
Aluminium/aluminium stulpverpakkings [aluminiumfoelie van kouevorm-stulpverpakking (deksel foelie) en kouevorm-stulpstrookkleminaat vir Alu Alu stulpverpakking (vormfoelie)] strokies (4 stulpverpakkingstrokies van 7 tablette) in 'n karton wat 28 filmbedekte tablette bevat.

Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
Geen spesiale vereistes.

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8 REGISTRASIENOMMER(S)
Cholmin 10: 49/7.5/0481
Cholmin 20: 49/7.5/0482
Cholmin 40: 49/7.5/0483
Cholmin 80: 49/7.5/0484

9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
16 Maart 2021

10 DATUM VAN HERSIENING VAN DIE TEKS