1.3.1.1 Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DUCETIM PLUS 10/10 tablets

DUCETIM PLUS 10/20 tablets

DUCETIM PLUS 10/40 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DUCETIM PLUS 10/10 tablet contains 10 mg ezetimibe and 10 mg simvastatin.

Contains sugar: Lactose monohydrate 60,42 mg and lactose anhydrous 6,84 mg

For full list of excipients, see section 6.1.

Each DUCETIM PLUS 10/20 tablet contains 10 mg ezetimibe and 20 mg simvastatin.

Contains sugar: Lactose monohydrate 81,82 mg and lactose anhydrous 62,68 mg

For full list of excipients, see section 6.1.

Each DUCETIM PLUS 10/40 tablet contains 10 mg ezetimibe and 40 mg simvastatin.

Contains sugar: Lactose monohydrate 124,63 mg and lactose anhydrous 174,37 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

DUCETIM PLUS 10/10 is a white, oblong tablet, with 8,0 mm ± 0,2 mm length and 4,4 mm ± 0,2 mm width.

DUCETIM PLUS 10/20 is a white, oblong tablet scored on one side, with 10,0 mm ± 0,2 mm length and 5,5 mm ± 0,2 mm width.

DUCETIM PLUS 10/40 is a white, oblong tablet, with 14,8 mm ± 0,2 mm length and 6,0 mm ± 0,2 mm width.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DUCETIM PLUS is indicated for:

Primary Hypercholesterolaemia

DUCETIM PLUS is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) and to moderately increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

DUCETIM PLUS is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

4.2. Posology and method of administration

Posology

Adults

The patient should be placed on a standard cholesterol-lowering diet before receiving DUCETIM PLUS and should continue on this diet during treatment with DUCETIM PLUS. The dosage should be individualised according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response.

DUCETIM PLUS should be taken as a single daily dose in the evening, with or without food. The dosage range is 10/10 mg/day through 10/80 mg/day.
If a patient requires a 10/80 mg/day dose, a suitable formulation containing 10 mg ezetimibe and 80 mg simvastatin as available in the South African market should be prescribed.

The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55 %) may be started at 10/40 mg/day. After initiation or titration of DUCETIM PLUS, lipid levels may be analysed after 2 weeks and dosage adjusted, if needed.

Dosage in patients with Homozygous Familial Hypercholesterolaemia

The recommended dosage for patients with Homozygous Familial Hypercholesterolaemia is DUCETIM PLUS 10/40 mg/day or 10/80 mg/day in the evening.

If a 10/80 mg/day dose is required, a suitable formulation containing 10 mg ezetimibe and 80 mg simvastatin as available in the South African market should be prescribed.

DUCETIM PLUS should be used as an adjunct to other lipid lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Special populations

Use in the elderly

No dosage adjustment is required for elderly patients.

Use in hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with DUCETIM PLUS is contraindicated as safety and efficacy have not been demonstrated in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score greater than 9) liver dysfunction (see section 4.3).

Use in renal impairment

No dosage adjustment is required for patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance less than or equal to 30 mL/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously.

Co-administration with other medicines

Dosing of DUCETIM PLUS should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant. In patients taking ciclosporin, danazol or greater than or equal to 1g/day of niacin concomitantly with DUCETIM PLUS, the dose of DUCETIM PLUS should not exceed 10/10 mg/day (see section 4.5).

In patients taking amiodarone or verapamil concomitantly with DUCETIM PLUS, the dose of DUCETIM PLUS should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

Paediatric population

Treatment with DUCETIM PLUS is contraindicated as safety and efficacy have not been demonstrated (see section 4.3).

Method of administration

For oral administration.

4.3. Contraindications

DUCETIM PLUS is contraindicated in:

- Patients with hypersensitivity to ezetimibe, statins such as simvastatin or to any excipients in DUCETIM PLUS (see section 6.1).

- Active liver disease or unexplained persistent elevations of serum transaminases, moderate to severe hepatic impairment.

- Pregnancy and lactation (see section 4.6).
- Children, as safety and efficacy have not been demonstrated.

- Concomitant administration of potent CYP3A4 inhibitors (medicines that increase AUC approximately 5 fold or greater) (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, and medicines containing cobicistat) (see sections 4.4 and 4.5).

- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 4.5).
- In patients with HoFH, concomitant administration of lomitapide with doses > 10/40 mg DUCETIM PLUS (see sections 4.2, 4.4 and 4.5).

4.4. Special warnings and precautions for use

The dose of DUCETIM PLUS should not exceed 10/10 mg daily in patients receiving concomitant medicine with greater than or equal to 1 g/day of niacin. The combined use of DUCETIM PLUS with medicines such as ciclosporin or danazol is contraindicated (see section 4.3). The dose of DUCETIM PLUS should not exceed 10/20 mg daily in patients receiving concomitant medicine with amiodarone or verapamil. The combined use of DUCETIM PLUS at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided.

Use of DUCETIM PLUS concomitantly with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors or nefazodone) is contraindicated.
If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with DUCETIM PLUS should be suspended during the course of treatment. Concomitant use with other medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided.

All patients starting therapy with DUCETIM PLUS, or whose dose of DUCETIM PLUS is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. DUCETIM PLUS therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms and/or a CK level

greater than 10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with DUCETIM PLUS or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

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 X ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Myopathy/Rhabdomyolysis

Simvastatin, as contained in DUCETIM PLUS, may cause myopathy manifested as muscle pain, tenderness or weakness with CK above 10 times the ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

• The risk of myopathy/rhabdomyolysis is increased by use of DUCETIM PLUS with the following:

Potent inhibitors of CYP3A4, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of DUCETIM PLUS (see section 4.5).

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting treatment in the following situations:

- elderly (age ≥ 65 years),

- female gender,
- renal impairment,
- uncontrolled hypothyroidism,
- personal or familial history of hereditary muscular disorders,
- previous history of muscular toxicity with a statin or fibrate,
- alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with any statin-containing medicines, such as DUCETIM PLUS, should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 X ULN), treatment should not be started.

Other medicines

Fibrates, or greater than or equal to 1 g/day of niacin, particularly with higher doses of DUCETIM PLUS (see section 4.5).

Ciclosporin or danazol particularly with higher doses of DUCETIM PLUS (see section 4.5). Amiodarone or verapamil with higher doses of DUCETIM PLUS (see section 4.5).

In an ongoing clinical trial, myopathy has been reported in 6 % of patients receiving simvastatin 80 mg and amiodarone.

Diltiazem

Patients on diltiazem treated concomitantly with ezetimibe 10 mg/simvastatin 80 mg had a slightly increased risk of myopathy. In clinical studies, the risk of myopathy in

patients taking simvastatin 40 mg with diltiazem was similar to that in patients taking simvastatin 40 mg without diltiazem (see section 4.5).

Fusidic acid

Patients on fusidic acid treated concomitantly with DUCETIM PLUS may have an increased risk of myopathy and rhabdomyolysis (see section 4.5**).**

• **The risk of myopathy/rhabdomyolysis is dose related for simvastatin.** In a clinical trial database in which 41 050 patients were treated with simvastatin, with 24 747, (approximately 60 %) treated for at least 4 years, the incidence of myopathy was approximately 0,02 %, 0,08 % and 0,53 % at 20, 40 and 80 mg/day, respectively. However, in these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Consequently

1. There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates, especially gemfibrozil. The safety and effectiveness of ezetimibe administered with fibrates have not been formally studied. **Therefore, the concomitant use of DUCETIM PLUS and fibrates should be avoided (see section 4.5).**

2. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking DUCETIM PLUS need closer monitoring. Therapy with DUCETIM PLUS should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

3. Patients on fusidic acid and DUCETIM PLUS should be closely monitored. Temporary suspension of DUCETIM PLUS treatment may be considered.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin, such as DUCETIM PLUS) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either medicine can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend DUCETIM PLUS in patients taking daptomycin.

Consult the prescribing information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) and for further guidance related to monitoring (see section 4.5).

Liver Enzymes

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (greater than or equal to 3 times the ULN) have been observed (see section 4.8). It is recommended that liver function tests be performed before treatment with DUCETIM PLUS begins and thereafter when clinically indicated. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the ULN and are persistent, the medicine should be discontinued. DUCETIM PLUS should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of DUCETIM PLUS.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, DUCETIM PLUS is not recommended in these patients.

Diabetes mellitus

Some evidence suggests that statins, as in DUCETIM PLUS, 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 > 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, including simvastatin, 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, DUCETIM PLUS therapy should be discontinued.

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of DUCETIM PLUS and fibrates is not recommended (see section 4.5).

Ciclosporin

Caution should be exercised when initiating DUCETIM PLUS in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving DUCETIM PLUS and ciclosporin (see section 4.5).

Anticoagulants

If DUCETIM PLUS is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see section 4.5).

Paediatric population

Safety and efficacy have not been demonstrated.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5. Interaction with other medicines and other forms of interaction

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin. DUCETIM PLUS is bioequivalent to co-administered ezetimibe and simvastatin.

CYP3A4 Interactions

It has been shown that ezetimibe, as contained in DUCETIM PLUS, does not induce cytochrome P450 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicine known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9 and 3A4, or N-acetyltransferase. Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of

other medicines metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of DUCETIM PLUS (see section 4.4). **Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone (see section 4.4).**

Interactions with lipid-lowering medicines that can cause myopathy when given alone (e.g. fibrates and niacin). The risk of myopathy is also increased by the following lipid lowering medicines that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone. **Fibrates and Niacin (nicotinic acid) (greater than or equal to 1 g/day) (see section 4.4).**

Other medicine interactions

Ciclosporin or danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin or danazol, particularly with higher doses of DUCETIM PLUS (see section 4.4).

Amiodarone or verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of DUCETIM PLUS (see section 4.4).

Amlodipine, elbasvir and grazoprevir

Do not exceed 10/20 mg DUCETIM PLUS daily.

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 L/day) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and administration of simvastatin in the evening also resulted in a 1,9-fold

increase. Intake of grapefruit juice during treatment with DUCETIM PLUS should therefore be avoided.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

Rifampicin

Rifampicin is a potent CYP3A4 inducer, patients undertaking long-term rifampicin (e.g. for the treatment of tuberculosis) may be experiencing loss of efficacy of simvastatin.

Colestyramine: Concomitant colestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental LDL-C reduction due to adding DUCETIM PLUS to colestyramine may be lessened by this interaction.

Diltiazem: Patients on diltiazem treated concomitantly with ezetimibe 10 mg/simvastatin 80 mg have a slightly increased risk of myopathy (see section 4.4).

Fusidic acid: Patients on fusidic acid treated concomitantly with DUCETIM PLUS may have an increased risk of myopathy and rhabdomyolysis (see section 4.4).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1,5 and 1,7 fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of DUCETIM PLUS administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical

study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of DUCETIM PLUS with fibrates is not recommended until use in patients is studied.

Anticoagulants: In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20 to 40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1,7 to 1,8 and from 2,6 to 3,4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting DUCETIM PLUS 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 coumarin anticoagulants. If the dose of DUCETIM PLUS is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants. Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione (see section 4.4). The effect of DUCETIM PLUS on the prothrombin time has not been studied.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Ciclosporin: In a study of eight post-renal transplant patients with creatinine clearance of greater than 50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3,4-fold (range 2,3 to 7,9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2 mL/min/1,73 m^2) who was receiving multiple medicines, including ciclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve healthy patients, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin, AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

DUCETIM PLUS is contraindicated during pregnancy (see section 4.3).
No controlled clinical trials with simvastatin have been conducted in pregnant women. Reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. The safety of DUCETIM PLUS in pregnant women has not been established. Maternal treatment with DUCETIM PLUS may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis.

For this reason, DUCETIM PLUS should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with DUCETIM

PLUS should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

No clinical data on exposed pregnancies are available for ezetimibe.

Breastfeeding

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active components of DUCETIM PLUS are excreted into human breast milk; therefore, women who are nursing should not take DUCETIM PLUS.

Fertility

Ezetimibe

No clinical trial data are available on the effects of ezetimibe on human fertility.

Ezetimibe had no effect on the fertility of male or female rats.

Simvastatin

No clinical trial data are available on the effects of simvastatin on human fertility.

Simvastatin had no effect on the fertility of rats male and female.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported (see section 4.8), therefore patients should exercise caution when driving or operating hazardous machinery.

4.8 Undesirable effects

a) *Tabulated list of adverse reactions*

Adverse events reported with the combination product (ezetimibe/simvastatin):

System organ class	Frequent	Less frequent
Nervous system disorders	Headache	
Gastrointestinal disorders	Flatulence	
Musculoskeletal and connective tissue disorders	Myalgia	
General disorders and administrative site conditions		Malaise, oedema peripheral
Investigations	Increased ALT and/or AST[1,2], increased blood CK [1,2]	Increased blood bilirubin[1,2] , increased blood uric acid[1,2] , increased gamma-glutamyltransferase[1,2], increased international normalised ratio[1,]; protein urine present[1], decreased weight[1]

[1,]Adverse reactions with DUCETIM PLUS and at a greater incidence than placebo
[2] Adverse reactions with DUCETIM PLUS and at a greater incidence than statins

Adverse events reported with ezetimibe:

System organ class	Frequent	Less frequent
Blood and the lymphatic system disorders		Thrombocytopenia
Psychiatric disorders		Depression,
Nervous system disorders		Dizziness, paraesthesia,
Gastrointestinal disorders	Abdominal pain, diarrhoea	Pancreatitis, nausea,
Hepato-biliary disorders		Hepatitis, cholelithiasis, cholecystitis increased CPK, elevations of liver transaminases
Skin and subcutaneous tissue disorders		Hypersensitivity reactions, including rash, and urticaria, anaphylaxis, and angio-oedema, erythema multiforme

Musculoskeletal and connective tissue disorders		Arthralgia, myopathy, rhabdomyolysis
General disorders and administrative site conditions	Fatigue	

Adverse events reported with simvastatin:

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Anaemia	
Psychiatric disorders		Insomnia	
Nervous system disorders		Dizziness, paraesthesia peripheral neuropathy, memory impairment	
Gastrointestinal disorders	abdominal pain, diarrhoea	Pancreatitis, nausea, constipation, dyspepsia, vomiting	
Hepato-biliary disorders		Hepatitis, jaundice/hepatic failure increased CPK,	
Skin and subcutaneous tissue disorders		rash, alopecia, pruritus,	
Musculoskeletal and connective tissue disorders		muscle cramps, myopathy, rhabdomyolysis	
General disorders and administrative site conditions			Asthenia

b) Description of selected adverse reactions

Musculoskeletal, connective tissue and bone disorders

An apparent hypersensitivity syndrome has been reported , which has included some of the following features: angio-oedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

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. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

Co-administration of ezetimibe (1 000 mg/kg) and simvastatin (1 000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD50 for both species was ezetimibe greater than or equal to 1 000 mg/kg, simvastatin greater than or equal to 1 000 mg/kg.

Ezetimibe: In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy patients for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin: A few cases of overdosage have been reported; the maximum dose taken was 3,6 g. All patients recovered without sequelae.

Treatment

No specific treatment of overdosage with DUCETIM PLUS can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: HMG CoA reductase inhibitors in combination with other lipid modifying agents.

ATC code: C10BA02

Mechanism of action

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol and related plant sterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver.

Ezetimibe in animals inhibited the absorption of [14C] -cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl oestradiol, or the fat-soluble vitamins A and D.

Simvastatin

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxy acid form which inhibits HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also decreases during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

5.2. Pharmacokinetic properties

Absorption

DUCETIM PLUS is bioequivalent to co-administered ezetimibe and simvastatin.

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets.

Simvastatin

The availability of the beta-hydroxy acid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the beta-hydroxy acid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are bound 99,7 % and 88 to 92 % to human plasma proteins, respectively.

Simvastatin

Both simvastatin and the beta-hydroxy acid are bound to human plasma proteins (95 %).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicine occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1,3 to 2,4 hours post-dose.

Biotransformation

Ezetimibe

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase II reaction) has been observed in all animal species evaluated. Ezetimibe and ezetimibe-glucuronide are the major medicine-derived compounds detected in plasma, constituting approximately 10 % to 20 % and 80 % to 90 % of the total medicine in plasma, respectively.

Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling.

The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Simvastatin

Simvastatin is an inactive lactone which is readily hydrolysed in *vivo* to the corresponding beta-hydroxy acid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow. In man, simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood

flow. The liver is its primary site of action, with subsequent excretion of medicine equivalents in the bile. Consequently, availability of active medicine to the systemic circulation is low.

Elimination

Ezetimibe

Following oral administration of 14C-ezetimibe (20 mg) to human patients, total ezetimibe accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Simvastatin

Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicine equivalents excreted in bile as well as unabsorbed medicine. Following an intravenous injection of the beta-hydroxy acid metabolite, an average of only 0,3 % of the IV dose was excreted in urine as inhibitors.

Characteristics in patients (special populations)

Elderly Patients

Ezetimibe

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (65 years or older) than in the young (18 to 45 years).

Simvastatin

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG CoA reductase inhibitory activity was increased approximately 45 % compared with 18 patients between 18 to 30 years of age.

Renal impairment

Ezetimibe

After a single 10 mg dose of ezetimibe as monotherapy in patients with severe renal disease (mean creatinine clearance (CrCl) less than or equal to 30 mL/min), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy patients.

An additional patient in this study (post-renal transplant and receiving multiple medicines, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Simvastatin

In a study of patients with severe renal insufficiency (creatinine clearance less than 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA 20 reductase inhibitor were approximately 2-fold higher than those in healthy volunteers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene, croscarmellose sodium, hypromellose, lactose anhydrous, lactose monohydrate and sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters enclosed in carton until required for use.

6.5 Nature and contents of container

Tablets are packed in white 254 µm polyvinylchloride/ 70 µm polyethylene, ethylene vinyl alcohol, polyethylene/102 µm clear, poly-chloro-tri-fluro-ethylene film sealed with Aluminium 20 µm with 10 tablets per blister strip. The blister strips are then packed into a cardboard carton containing 30 tablets per pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8 REGISTRATION NUMBER

DUCETIM PLUS 10/10: 54/7.5/0690

DUCETIM PLUS 10/20: 54/7.5/0691

DUCETIM PLUS 10/40: 54/7.5/0692

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10 DATE OF REVISION OF TEXT

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