APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DYTOREZ 10/10 film coated tablets

DYTOREZ 10/20 film coated tablets

DYTOREZ 10/40 film coated tablets

DYTOREZ 10/80 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DYTOREZ 10/10: Each film coated tablet contains 10 mg ezetimibe and atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin.

DYTOREZ 10/20: Each film coated tablet contains 10 mg ezetimibe and atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin.

DYTOREZ 10/40: Each film coated tablet contains 10 mg ezetimibe and atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin.

DYTOREZ 10/80: Each film coated tablet contains 10 mg ezetimibe and atorvastatin calcium trihydrate equivalent to 80 mg atorvastatin.

DYTOREZ contains sugar (lactose monohydrate and lactose anhydrous) in the following quantities:

DYTOREZ 10/10 (171,15 mg; 13,7 mg), DYTOREZ 10/20 (171,15 mg; 27,4 mg), DYTOREZ 10/40 (171,15 mg; 54,8 mg) and DYTOREZ 10/80 (171,15 mg; 109,6 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

DYTOREZ 10/10: White to off-white capsule-shaped, bi-convex, film coated tablet debossed with 'AE' on one side and ‘1’ on the other side.

DYTOREZ 10/20: White to off-white capsule-shaped, bi-convex, film coated tablet debossed with 'AE' on one side and '2' on the other side.

DYTOREZ 10/40: White to off-white capsule-shaped, bi-convex, film coated tablet debossed with 'AE' on one side and '3' on the other side.

DYTOREZ10/80: White to off-white capsule-shaped, biconvex, film coated tablet debossed with 'AE' on one side and ' ' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

DYTOREZ, administered with an HMG-CoA reductase inhibitor (statin) or alone, is

indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

DYTOREZ is indicated as adjunctive therapy to diet for use in adults to reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolaemia (HoFH).

4.2 Posology and method of administration

Posology

The patient should be on an appropriate lipid-lowering diet and weight loss programme where indicated and should continue on this diet during treatment with DYTOREZ.

The usual starting dose of DYTOREZ is 10/10 mg once a day and atorvastatin dosage 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 dose will depend on the indication (see below).

Primary Hypercholesterolaemia and Combined (mixed) Hyperlipidaemia

The majority of patients are controlled with 10/10 mg DYTOREZ 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.

Homozygous Familial Hypercholesterolaemia

The dose of DYTOREZ in patients with homozygous familial hypercholesterolaemia is 10/10 to 10/40 mg daily. DYTOREZ may be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Co-administration with bile acid sequestrants

Dosing of DYTOREZ should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant.

Co-administration with other medicines

In patients taking hepatitis C antiviral medicines elbasvir/grazoprevir concomitantly with DYTOREZ, the dose of DYTOREZ should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

Special populations

Elderly

No dosage adjustment is required for elderly patients (see section 5.2).

Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with DYTOREZ is contraindicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction due to unknown effects (see sections 4.3 and 5.2).

In patients with moderate to severe hepatic dysfunction, the therapeutic response to atorvastatin is unaffected but serum levels of the atorvastatin 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 Childs-Pugh B disease. Therefore, caution with dosage should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see sections 4.3 and 5.2).

Renal Impairment

Renal disease has no influence on the plasma concentrations or on the lipid effects of DYTOREZ; thus, no adjustment of dose is required.

Paediatric population

No clinical data on safety and efficacy are available; therefore, treatment with DYTOREZ is contraindicated.

Method of administration

DYTOREZ is for oral administration and can be administered at any time of the day, with or without food.

4.3 Contraindications

- hypersensitivity to atorvastatin, ezetimibe or to any of the ingredients of DYTOREZ listed in section 6.1
- pregnancy, as no clinical data on exposed pregnancies is available
- lactation, as it is not known whether ezetimibe is excreted into human breast milk
- women of child-bearing potential not using appropriate contraceptive measures
- moderate to severe hepatic impairment (Child Pugh score 7 or more) and active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (see section 4.4)
- patients with Child-Pugh B and C (liver cirrhosis)
- concomitant use with rifampicin, diltiazem and grapefruit juice (see section 4.4)
- DYTOREZ is contraindicated in patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

Liver effects

Persistent elevations (> 3 times the upper limit of normal (ULN) which occurred on 2 or more occasions) in serum transaminases occurred in 0,7 % of patients who received atorvastatin, as in DYTOREZ, in clinical trials. The incidence of these abnormalities was 0,2 %, 0,2 %, 0,6 % and 2,3 % for 10, 20, 40 and 80 mg respectively.

It is recommended that liver function tests be performed before the initiation of treatment and repeated as clinically indicated.

In controlled co-administration trials in patients receiving ezetimibe with a statin, as in DYTOREZ, consecutive transaminase elevations (≥ 3 x ULN) have been observed.

If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with DYTOREZ, promptly interrupt therapy. If an alternate aetiology is not found, do not restart DYTOREZ.

DYTOREZ should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of DYTOREZ (see section 4.3).

Skeletal Muscle

In clinical trials the incidence of CPK > 10 x ULN was 0,2 % for ezetimibe, as in DYTOREZ, versus 0,1 % for placebo and 0,1 % for ezetimibe co-administered with a statin versus 0,4 % for statins alone.

Cases of myopathy and rhabdomyolysis have been reported. All patients starting therapy with DYTOREZ should be advised of the risk of myopathy and to report promptly any unexplained muscle pain (diffuse myalgias), tenderness or weakness, particularly if accompanied by malaise or fever. DYTOREZ should be immediately discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level greater than 10 times the ULN indicates myopathy.

Myalgia has been reported in patients treated with atorvastatin (see section 4.6).

Rhabdomyolysis with or without renal impairment has also been reported with the use of atorvastatin. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

The risk of myopathy during treatments with DYTOREZ is increased with concurrent administration of immunosuppressive medicines including ciclosporin, fibric acid derivatives, nicotinic acid, azole antifungals or erythromycin, colchicine, the hepatitis C protease inhibitor telaprevir, boceprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir and cytochrome

P450 inhibitors (see section 4.5). Medical practitioners considering combined therapy with DYTOREZ and fibric acid derivatives, erythromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, immunosuppressive medicines, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either medicine. Muscle-related adverse events have been reported with concomitant DYTOREZ and fusidic acid. Temporary suspension of DYTOREZ may be appropriate during fusidic acid therapy (see section 4.5).

DYTOREZ therapy should be withdrawn in any patient 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).

Haemorrhagic Stroke

In a post-hoc analysis of a clinical study, patients without coronary heart disease (CHD) who had a stroke or transient ischaemic attack (TIA) within the preceding 6 months who were initiated on atorvastatin 80 mg, revealed a higher incidence of haemorrhagic stroke compared to placebo. Patients with haemorrhagic stroke on entry appeared to be at increased risk for recurrent haemorrhagic stroke.

Fibrates

The safety and efficacy of DYTOREZ administered with fibrates have not been established. The co-administration of DYTOREZ with fibrates other than fenofibrate has not been studied.

Fenofibrate

If cholelithiasis is suspected in a patient receiving DYTOREZ and fenofibrate, gallbladder studies are indicated, and alternative lipid-lowering therapy should be considered (see section 4.8 and the Professional Information for fenofibrate).

Ciclosporin

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

Anticoagulants

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

Protease inhibitors

Co-administration of atorvastatin, as in DYTOREZ, and protease inhibitors was associated with increased plasma concentrations of atorvastatin.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. atorvastatin and ezetimibe/atorvastatin) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend DYTOREZ in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. Consult the prescribing information of Daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. atorvastatin and ezetimibe/atorvastatin) and for further guidance related to monitoring. (See section 4.5).

Endocrine function

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

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.

Lactose

DYTOREZ contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DYTOREZ.

4.5 Interaction with other medicines and other forms of interaction

Ezetimibe does not induce cytochrome P450 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Ezetimibe had no significant effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, midazolam or warfarin during co-administration. However, there have been post-marketing reports of increased International Normalised Ratio in patients who had ezetimibe added to warfarin. Most of these patients were also on other medication. If ezetimibe is added to warfarin or another coumarin anticoagulant, the International Normalised Ratio (INR) should be appropriately monitored (see section

4.4). Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

The risk of myopathy during treatment with DYTOREZ is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, niacin (nicotinic acid) or cytochrome P450 3A4 inhibitors (macrolide antibiotics e.g. erythromycin, and azole antifungals e.g. clotrimazole)

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolised by cytochrome P450 3A4. Concomitant administration of DYTOREZ with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4 (see section 4.4).

Inducers of cytochrome P450 3A:

Concomitant administration of DYTOREZ with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin, simultaneous co-administration of DYTOREZ with rifampicin is not recommended, as delayed administration of DYTOREZ after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacids

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

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin approximately 35 %; however, LDL-C reduction was not altered.

Cholestyramine

Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe by approximately 55 %. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction.

Fibrates

Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations by approximately 1,5 and 1,7-fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of DYTOREZ administered with fibrates have not been established. The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see section 4.5). Co-administration of DYTOREZ with other fibrates has not been studied. 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 DYTOREZ with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Transporter inhibitors

In a study of 8 post renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of cyclosporin, 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 historical healthy control population. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2mL/min/1,73m^2) who was receiving multiple medications including cyclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve heathy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of cyclosporin alone (see section 4.4).

Inhibitors of the OATP1B1 (e.g. ciclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and ciclosporin 5,2 mg/kg/day resulted in an 8,7-fold increase in exposure to atorvastatin.

Erythromycin/Clarithromycin

In healthy individuals, plasma concentrations of atorvastatin increased approximately 40

% with co-administration of atorvastatin, as in DYTOREZ, and erythromycin, a known inhibitor of cytochrome P450 3A4 (see section 4.4- Skeletal Muscle).

Combination of Protease Inhibitors

Plasma concentrations of atorvastatin increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of DYTOREZ should be avoided. Concomitant administration of atorvastatin 10 mg single dose with tipranavir 500 mg twice daily plus ritonavir 200 mg twice daily for seven days, resulted in a 9,4-fold increase in atorvastatin AUC and 8,6-fold increase in atorvastatin C_{max}. Atorvastatin did not result in a change in pharmacokinetics of tipranavir plus ritonavir. Concomitant administration of atorvastatin 20 mg single dose with telaprevir 750 mg every eight hours, for 10 days, resulted in a 7,9-fold increase in atorvastatin AUC and 10,6-fold increase in atorvastatin C_{max}.

In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing DYTOREZ and the lowest dose necessary should be used. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5,9-fold increase in atorvastatin AUC. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir,

fosamprenavir, or fosamprenavir plus ritonavir, the dose of DYTOREZ should not exceed 10/20 mg and should be used with caution. Concomitant administration of atorvastatin 40 mg once a day for 4 days with saquinavir 400 mg twice daily plus ritonavir 400 mg twice daily for 15 days resulted in a 3,9-fold increase in atorvastatin AUC and 4,3-fold increase in atorvastatin C_{max}. The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used. Concomitant administration of atorvastin 10 mg once a day for 4 days with darunavir 300 mg twice daily plus ritonavir 100 mg twice daily for 9 days resulted in a 3,4-fold increase in atorvastatin AUC and 2,3-fold increase in atorvastatin C_{max}. Concomitant administration of atorvastatin 10 mg once a day for 4 days with fosamprenavir 1 400 mg twice a day for 14 days resulted in a 2,3-fold increase in atorvastatin AUC and 4,0-fold increase in atorvastatin C_{max}. Atorvastatin resulted in a 1,27-fold increase in fosamprenavir. Concomitant administration of atorvastatin 10 mg once a day for 4 days with fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day for 14 days resulted in a 2,5-fold increase in atorvastatin AUC and 2,8-fold increase in atorvastatin C_{max}. Atorvastatin did not result in a change in pharmacokinetics of fosamprenavir 700 mg plus ritonavir.

In patients taking nelfinavir, the dose of DYTOREZ should not exceed 10/40 mg daily. Concomitant administration of atorvastatin 10 mg once a day for 28 days with nelfinavir 1 250 mg twice a day for 14 days resulted in a 74 % increase in atorvastatin AUC and 2,2-

fold increase in atorvastatin C_{max}.

Concomitant administration of atorvastatin 40 mg single dose with boceprevir 800 mg three times a day for 7 days resulted in a 2,3-fold increase in atorvastatin AUC and 2,66-fold increase in atorvastatin C_{max} (see section 4.4 – Skeletal muscle).

Inhibitors of Breast Cancer Resistant Protein (BCRP):

Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy; therefore, a dose adjustment of atorvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with atorvastatin increases plasma concentrations of atorvastatin 1,9-fold; therefore, the dose of DYTOREZ should not exceed 10/20 mg daily in patients receiving concomitant medications with products containing elbasvir or grazoprevir (see sections 4.2 and 4.4).

Diltiazem hydrochloride

Co-administration of DYTOREZ, with diltiazem was associated with an increase in AUC of 51 % of atorvastatin (see section 4.5).

Cimetidine

Cimetidine co-administered with DYTOREZ, had no effect on the bioavailability of

ezetimibe and the atorvastatin plasma concentrations and LDL-C reduction were not altered.

Itraconazole

Co-administration of atorvastatin 40 mg, single dose and itraconazole 200 mg, once daily, was associated with a 3,3-fold increase in AUC and a 20 % increase in C_{max}.

Grapefruit juice

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

Antipyrine

Because DYTOREZ does not affect the pharmacokinetics of antipyrine interactions with other drugs metabolized via the same cytochrome isoenzymes are not expected.

Colestipol

Plasma concentrations of atorvastatin decreased approximately 25 % when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin, as in DYTOREZ, and colestipol were co-administered than when either medicine was given alone.

Digoxin

Co-administration of multiple doses of atorvastatin, as in DYTOREZ, and digoxin increased steady-state plasma digoxin concentrations by approximately 20 %. Patients taking digoxin should be monitored appropriately (see section 4.4).

Azithromycin

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

Oral contraceptives

Co-administration of atorvastatin and an oral contraceptive increased AUC-values of norethindrone and ethinyl estradiol approximately 30 % and 20 %, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking DYTOREZ.

Anticoagulants

There have been reports of increased International Normalised Ratio in patients who had ezetimibe added to warfarin. Most of these patients were also on other medication. Atorvastatin had no clinically significant effect on prothrombin/INR time when administered to patients receiving combined atorvastatin and warfarin therapy for two

weeks.

If DYTOREZ is added to warfarin or another coumarin anticoagulant, the International Normalised Ratio (INR) should be appropriately monitored (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 DYTOREZ with colchicine.

Amlodipine

Atorvastatin pharmacokinetics were not altered by the co-administration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

Fusidic acid

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

Other Concomitant Therapy

In clinical studies, atorvastatin was used concomitantly with antihypertensive medicine and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific medicine have not been conducted.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

DYTOREZ should be administered to women of childbearing age only when such patients are using adequate contraception and have been informed of the potential hazards to the foetus. An interval of one month should be allowed from stopping DYTOREZ treatment to conception in the event of planning a pregnancy.

Pregnancy

DYTOREZ is contraindicated in pregnancy as no clinical data on exposed pregnancies are available (see section 4.3).

Breastfeeding

The use of DYTOREZ is not recommended during lactation, as it is not known whether ezetimibe is excreted into human breast milk (see section 4.3).

Fertility

No fertility studies were conducted.

4.7 Effects on ability to drive and use machines:

No studies of the effects on the ability to drive and use of machines have been performed. However, certain side effects such as dizziness that have been reported with DYTOREZ may affect some patients' ability to drive or operate machinery. Individual responses to DYTOREZ may vary (see section 4.8).

4.8 Undesirable effects

a. Tabulated list of adverse effects

Ezetimibe

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Viral infection, pharyngitis, sinusitis, upper respiratory tract infection
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Hypersensitivity reactions, including anaphylaxis, rash, urticaria, angioedema
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequency unknown	Paraesthesia

Respiratory, thoracic and mediastinal disorders	Less frequent	Coughing
Gastrointestinal disorders	Frequent Frequency unknown	Abdominal pain, diarrhoea Nausea, pancreatitis
Hepatobiliary disorders	Frequency unknown	Hepatitis, cholelithiasis cholecystitis
Skin and subcutaneous tissue disorders	Frequency unknown	Erythema multiforme
Musculoskeletal and connective tissue disorders	Less frequent Frequency unknown	Arthralgia, back pain, myalgia Myopathy, rhabdomyolysis
General disorders and administrative site conditions	Frequent Less frequent	Headache Fatigue, chest pain, dizziness
Investigations	Frequency unknown	increased transaminases, increased CPK

Atorvastatin

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Less frequent	Infection, flu syndrome, sinusitis, pharyngitis

Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Frequent	Allergic reaction (including anaphylaxis)
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia, hyperglycaemia, anorexia, weight gain
Psychiatric disorders	Frequent Frequency unknown	Insomnia Cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion)
Nervous system disorders	Frequent Less frequent	Hypoesthesia, paraesthesia, dizziness Peripheral neuropathy, amnesia, dysgeusia
Ear and labyrinth disorders	Less frequent	Tinnitus
Gastrointestinal disorders	Frequent Less frequent	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence Vomiting, pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis, cholestatic jaundice

Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash Alopecia, urticaria, bullous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Myalgia, arthralgia, back pain Myositis, muscle cramps, rhabdomyolysis, myopathy Immune-mediated necrotizing myopathy
Reproductive system and breast disorders	Less frequent	Impotence
General disorders and administrative site conditions	Frequent Less frequent	Asthenia, chest pain, headache Malaise, peripheral oedema, fatigue
Injury, poisoning and procedural complications	Less frequent	Tendon rupture, accidental injury

Ezetimibe/atorvastatin combination

System Organ Class	**Frequency**	**Side effects**

Infections and infestations	Less frequent Frequency unknown	Influenza, bronchitis, sinusitis Nasopharyngitis, urinary tract infection, infection, pharyngitis
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria
Metabolism and nutrition disorders	Less frequent Frequency unknown	Hyperkalaemia Decreased appetite, anorexia, hyperglycaemia; hypoglycaemia
Psychiatric disorders	Less frequent Frequency unknown	Depression, insomnia, sleep disorder Nightmares
Nervous system disorders	Less frequent Frequency unknown	Dizziness, dysgeusia, paraesthesia, headache Hypoesthesia, amnesia, peripheral neuropathy
Eye disorders	Frequency unknown	Vision blurred
Ear and labyrinth disorders	Frequency unknown	Tinnitus, deafness
Cardiac disorders	Less frequent	Sinus bradycardia

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Vascular disorders	Less frequent Frequency unknown	Hot flushes Hypertension, haemorrhagic stroke
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Dyspnoea, coughing Pharyngolaryngeal pain, epistaxis, asthma
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Abdominal pain, constipation, diarrhoea, flatulence, nausea Abdominal discomfort, frequent bowel movements, stomach discomfort, upset stomach, abdominal distension, dyspepsia, gastritis Pancreatitis, gastroesophageal reflux disease, eructation, vomiting, dry mouth
Hepato-biliary disorders	Frequency unknown	Hepatitis, cholelithiasis, cholecystitis, hepatic failure, cholestasis
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Acne, urticaria Pruritus, skin rash, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrosis), alopecia

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Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Myalgia Arthralgia, back pain, muscle fatigue, muscle weakness, pain in extremities, muscle spasms, musculoskeletal stiffness Immune mediated necrotising myopathy, myopathy/rhabdomyolysis which may be fatal, neck pain, joint swelling, musculoskeletal pain, myositis
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia, erectile dysfunction
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Fatigue Asthenia, oedema, malaise, increased weight Chest pain, pain, peripheral oedema, pyrexia

Investigations	Frequent	Increased alanine transaminase (ALT), increased aspartate transaminase (AST)
	Less frequent	Increased alkaline phosphatase, gamma-glutamyltransferase, and hepatic enzyme, abnormal liver function test, increased blood CK
	Frequency unknown	Positive white blood cells in urine
Injury, poisoning and procedural complications	Frequency unknown	Tendon rupture, injury

B. Description of selected adverse reactions

Laboratory Values

In controlled clinical monotherapy trials, the incidence of clinically significant elevations in serum transaminases (ALT and/or AST greater than or equal to 3 X the upper limit of normal (ULN), consecutive) was not statistically different between ezetimibe (0,5 %) and placebo (0,3 %). In co-administration trials, the incidence was 1,3% for patients treated with ezetimibe co-administered with a statin and 0,4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link :

https://www.sahpra.org.za/Publications/Index/8

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za.

4.9 Overdose

Management of overdose:

In the event of an overdose, symptomatic and supportive measures should be employed. In clinical studies administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated.

Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Lipid modifying agents, combinations

ATC code: C10BA05

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Pharmacological classification: A7.5 Serum-cholesterol reducers

5.1 Pharmacodynamic properties

Mechanism of action

DYTOREZ (ezetimibe/atorvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. DYTOREZ contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. Together these distinct mechanisms reduce total-C, LDL-C, Apo B, TG, and non-HDL-C, and increase HDL-C beyond either treatment alone, through dual inhibition of cholesterol absorption and synthesis.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

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Ezetimibe

In human studies, ezetimibe inhibited the intestinal absorption of cholesterol and related plant sterols.

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

The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols. Ezetimibe therefore inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

Atorvastatin

Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glytaryl-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. Triglycerides (TG) and cholesterol in the liver are incorporated into very low-density lipoprotein (VLDL) and

released into the plasma for delivery to peripheral tissues. Low density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of 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 change in the quality of circulating LDL-C particles.

Atorvastatin reduces total cholesterol (total-C), LDL-C, apolipoprotein-B (apo-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 and produces variable increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A-1 in non-familial hypercholesterolaemia and mixed dyslipidaemias.

5.2 Pharmacokinetic properties

Absorption:

Ezetimibe: After oral administration, ezetimibe is absorbed and extensively conjugated to

a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) 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 availability of ezetimibe when administered as ezetimibe 10 mg tablets. Ezetimibe can be administered with or without food.

Atorvastatin: Following oral administration; maximum plasma concentrations occur within 1 to 2 hours. The absolute bioavailability of atorvastatin (parent substance) is approximately 12 % and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug 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 drug administration compared to morning administration. However, LDL-C reduction is the same regardless of the time of drug administration (see section 4.2).

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Distribution:

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

Atorvastatin: Mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is 98 % or more bound to plasma proteins.

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 I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine in the plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant entero-hepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Atorvastatin: Atorvastatin is extensively metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70 % of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination:

Ezetimibe: Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) 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.

Atorvastatin: 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 (parent substance) 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

Pharmacokinetics in special patient groups

Elderly

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

Plasma concentrations of atorvastatin are higher (approximately 40 % for C_{max} and 30 %

for AUC) in healthy elderly subjects (65 years and older) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of atorvastatin.

Gender

Plasma concentrations for total ezetimibe are slightly higher (< 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Plasma concentrations of atorvastatin in women differ (approximately 20 % higher for C_{max} and 10 % lower for AUC) from those in men; however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Race

Based on meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between black and white subjects.

Hepatic Insufficiency:

After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1,7- fold in patients with mild hepatic

insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic insufficiency, ezetimibe is contra-indicated in these patients.
Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B). See section 4.3.

Renal Insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8, mean creatinine clearance (CrCl) $\leq$ 30 mL/min/1,73 m^2), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects (n=9).
An additional patient in this study (post-renal transplant and receiving multiple medications, including cyclosporin) had a 12-fold greater exposure to total ezetimibe (see section 4.5).
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).

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 drug is extensively bound to plasma proteins.

Paediatric population

The absorption and metabolism of ezetimibe are similar between children 10 years of age or older adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population less than 10 years of age are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cores

Calcium carbonate

Colloidal anhydrous silica

Crospovidone

Hydroxy propyl cellulose

Lactose anhydrous

Lactose monohydrate

Microcrystalline cellulose

Povidone

Sodium lauryl sulphate

Sodium stearyl fumarate

Coating

Opadry White AMB consisting of:

Lecithin

Polyvinyl alcohol

Talc

Titanium dioxide

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25˚C.

6.5 Nature and contents of container

30's pack: Cold form Alu/Alu: Laminated Aluminium foil, one side bright and shinning, the other side relatively dull for cold forming blister pack., 10 tablets per blister, enclosed in a carton box.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

DYTOREZ 10/10: 54/7.5/0326

DYTOREZ 10/20: 54/7.5/0327

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DYTOREZ 10/40: 54/7.5/0328

DYTOREZ 10/80: 54/7.5/0329

9. DATE OF FIRST AUTHORISATION

24 January 2023

10. DATE OF REVISION OF THE TEXT