PROFESSIONAL INFORMATION FOR DEZZOLIP TABLETS

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

DEZZOLIP 10 (film coated tablet)

DEZZOLIP 20 (film coated tablet)

DEZZOLIP 40 (film coated tablet)

DEZZOLIP 80 (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSTION

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

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

DEZZOLIP 40: Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 40 mg atorvastatin.

DEZZOLIP 80: Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 80 mg atorvastatin.

DEZZOLIP 10 contains sugar (mannitol 70,97 mg/tablet)

DEZZOLIP 20 contains sugar (mannitol 141,94 mg/tablet)

DEZZOLIP 40 contains sugar (mannitol 283,88 mg/tablet)

DEZZOLIP 80 contains sugar (mannitol 567,76 mg/tablet)

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

DEZZOLIP 10: White colored, oval shaped, biconvex film coated tablets with one side embossed “10” and other side plain.

DEZZOLIP 20: White colored, oval shaped, biconvex film coated tablets with one side embossed “20” and other side plain.

DEZZOLIP 40: White colored, oval shaped, biconvex film coated tablets with one side embossed “40” and other side plain

DEZZOLIP 80: White colored, oval shaped, biconvex film coated tablets with one side embossed “80” and other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Hypercholesterolaemia

DEZZOLIP is indicated:

- As an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglyceride levels in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) and combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.
- To reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if there are no treatments available.

b) Paediatric Patients (10 – 17 years old)

DEZZOLIP is indicated as an adjunct to diet to reduce total-C, LDL-C, and apolipoprotein B levels in boys and postmenarchal girls between 10 to 17 years old, with heterozygous familial

hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present:

1) LDL-C remains ≥ 190 mg/dℓ (4,98 mmol/ℓ) or
2) LDL-C remains ≥ 160 mg/dℓ (4,04 mmol/ℓ) and
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the paediatric patient.

c) Prevention of cardiovascular complications

In patients without clinically evident cardiovascular disease, and with or without dyslipidaemia, but with multiple risk factors for coronary heart disease, DEZZOLIP is indicated to reduce the risk of ischaemic cardiovascular and cerebrovascular diseases.

Secondary Prevention

DEZZOLIP is indicated in the prevention 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 DEZZOLIP, secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other medicine therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG.

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving DEZZOLIP and should continue on this diet during treatment with DEZZOLIP.

The usual starting dose is 10 mg once a day and should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum recommended dose will depend on the indication (see below). Doses may be given any time of the day with or without food.

Primary hypercholesterolaemia and combined hyperlipidaemia

The majority of patients are controlled with 10 mg DEZZOLIP once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia in paediatric patients (> 10 – 17 years old)

Patients should be started with 10 mg DEZZOLIP 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 DEZZOLIP, with a greater than 15 % reduction in LDL-C (18 % - 45 %).

Prevention of cardiovascular complications

The dosage range is 10 to 80 mg once daily.

Dosage in patients with renal insufficiency

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

Dosage in patients with hepatic dysfunction

In patients with moderate to severe hepatic dysfunction, the therapeutic response to DEZZOLIP 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 each 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 consume substantial quantities of alcohol and/or have a history of liver disease (See 4.3 and 4.4).

4.3 Contraindications

- Hypersensitivity to atorvastatin or to any of the ingredients of DEZZOLIP.
- Active liver disease or unexplained persistent increase of serum transaminases exceeding 3 times the upper limit of normal (See 4.4).
- Concomitant use with rifampicin, diltiazem and grapefruit juice.
- Patients with Child-Pugh B and C (liver cirrhosis).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Liver effects:

It is recommended that liver function tests should be performed before initiating treatment and periodically thereafter. Furthermore, patients who develop any signs or symptoms suggestive of liver injury should also have liver function tests performed.

Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in transaminases (ALT or AST) of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of DEZZOLIP is recommended.

DEZZOLIP 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 contra-indications to the use of DEZZOLIP.

Skeletal Muscle:

DEZZOLIP may affect the skeletal muscle and cause myalgia (generalised muscle pain), myositis (inflammation of muscle tissue), and myopathy (muscle aching or muscle weakness) that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal. DEZZOLIP should be discontinued if CPK increases significantly or if myopathy is diagnosed.

The risk of myopathy during treatment with DEZZOLIP is increased with concomitant use of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, nicotinic acid, azole antifungals or erythromycin, and cytochrome P450 inhibitors (See 4.5).

DEZZOLIP 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).

DEZZOLIP should be used with caution in patients with renal impairment as the risk of myopathy is increased.

Before the treatment

DEZZOLIP should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine kinase (CK) level should be measured before starting 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 and special populations including genetic subpopulations.

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 re-measured within 5 to 7 days later to confirm the results.

Whilst on treatment:

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

- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of DEZZOLIP or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- DEZZOLIP must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Protease inhibitors

Co-administration of DEZZOLIP and protease inhibitors increases plasma concentrations of DEZZOLIP.

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.

Increase in glycosylated haemoglobin (HbAIB) and fasting serum glucose levels have been reported with statin use.

4.5 Interaction with other medicines and other forms of interaction

The most serious consequence of interactions with DEZZOLIP is the development of myopathy or rhabdomyolysis. Medicines that cause myopathy when given alone increase the risk of

myopathy with DEZZOLIP; these medicines include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by medicines that increase the plasma concentrations of DEZZOLIP, by inhibiting their metabolism or by inhibiting their uptake into the liver.

Inhibitors of cytochrome P450 3A4:

DEZZOLIP is metabolised by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with medicines that inhibit this enzyme, including immunosuppressants (ciclosporin), itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, danazol, amiodarone, and verapamil. There may also be a similar interaction with grapefruit juice. Such combinations should be used with caution, if at all, and dose reduction may be revised.

Rhabdomyolysis may be reported when atorvastatin is given with the non-nucleoside reverse transcriptase inhibitor delavirdine.

Rhabdomyolysis and hepatitis have also been reported in patients receiving atorvastatin with diltiazem.

Inducers of cytochrome P450 3A4:

Concomitant administration of DEZZOLIP with inducers of cytochrome P450 isoenzyme CYP3A4 (e.g. efavirenz, rifampicin, St. John’s Wort) can lead to variable reductions in the plasma concentrations of DEZZOLIP. Due to the dual interaction mechanism of rifampicin, simultaneous co-administration of DEZZOLIP with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in DEZZOLIP plasma concentrations.

Antacids:

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides decreases plasma concentrations of DEZZOLIP approximately 35 %, however, LDL-

C reduction is not altered.

Colestipol:

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

Digoxin:

Co-administration of multiple doses of DEZZOLIP and digoxin increased steady-state plasma digoxin concentrations. Patients taking digoxin should be monitored appropriately.

Oral contraceptives:

Co-administration of DEZZOLIP with an oral contraceptive produces increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin:

Prothrombin time should be determined before starting DEZZOLIP in patients taking warfarin or other oral anticoagulants 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 or other oral anticoagulants. If the dose of DEZZOLIP is changed or discontinued, the same procedure should be repeated.

4.6 Fertility, pregnancy and lactation

DEZZOLIP is contraindicated in pregnancy, during breastfeeding and in women of child-bearing potential (See 4.3). Women of child-bearing potential should use appropriate contraceptive measures during treatment. An interval of one month should be allowed from stopping DEZZOLIP treatment to conception in the event of planning a pregnancy.

Treatment with DEZZOLIP should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

4.7 Effects on ability to drive or use machines

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

4.8 Undesirable effects

Infections and infestations

Frequent: Nasopharyngitis

Blood and lymphatic system disorders

Less frequent: Thrombocytopenia

Immune system disorders

Frequent: Allergic reactions (including anaphylaxis), angioedema

Metabolism and nutrition disorders

Less frequent: Hypoglycaemia, hyperglycaemia, anorexia, weight gain

Psychiatric disorders

Less frequent: Nightmare, insomnia, memory loss, forgetfulness, confusion

Nervous system disorders

Frequent: Hypoaesthesia, paraesthesia, dizziness, headache

Less frequent: Peripheral neuropathy, amnesia, dysgeusia

Eye disorders

Less frequent: Blurred vision, visual disturbances

Ear and labyrinth disorders

Less frequent: Tinnitus, hearing loss

Gastrointestinal disorders

Frequent: Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence

Less frequent: Vomiting, eructation, pancreatitis

Hepato-biliary disorders

Less frequent: Hepatitis, cholestatic jaundice, hepatic failure

Skin and subcutaneous tissue disorders

Frequent: Pruritus, rash

Less frequent: Alopecia, urticaria, bullous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal, connective tissue and bone disorders

Frequent: Myalgia, arthralgia, back pain

Less frequent: Myositis, muscle cramps, rhabdomyolysis, myopathy, neck pain, muscle fatigue, tendonopathy, sometimes complicated by rupture

Reproductive system and breast disorders

Less frequent: Impotence, gynaecomastia

General disorders and administrative site conditions

Frequent: Asthenia, chest pain

Less frequent: Malaise, peripheral oedema, fatigue, pyrexia

Investigations

Frequent: Abnormal liver function test, increased blood creatine kinase

Less frequent: Positive white blood cells urine

Injury and poisoning

Less frequent: Tendon rupture

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DEZZOLIP is important. It allows continued monitoring of the benefit/risk balance of DEZZOLIP. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

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

Report all side effects to Unicorn Pharmaceuticals (Pty) Ltd at enquiries@unicornpharma.co.za

By reporting side-effects, you can help provide more information on the safety of DEZZOLIP.

4.9 Overdose

Symptoms

There is no specific treatment available for DEZZOLIP overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological Class: A 7.5 Serum-cholesterol reducers

5.1 Pharmacodynamic properties

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that is responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Statins exert their major effect by a reduction of low-density lipoprotein (LDL) levels. LDL is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin reduces the levels of plasma cholesterol and lipoprotein 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, thereby providing for enhanced uptake and catabolism of LDL-C.

Atorvastatin produces an increase in LDL receptor activity together with a change in the quality of circulating LDL particles. The greater number of LDL receptors on the surface of hepatocytes results in increased removal of LDL from the blood, thereby lowering LDL-C levels.

Atorvastatin lowers total cholesterol (total-C), LDL-C, apolipoprotein B levels 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 including mixed dyslipidaemias.

5.2 Pharmacokinetic properties

Atorvastatin is well absorbed following oral administration where maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. The extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95 % to 99 % bioavailable compared to the oral solution. 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 due to the 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. However, there is no change in LDL-C reduction regardless of the time of administration (See 4.2).

Distribution

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

Metabolism

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.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, it does not appear to undergo significant 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 approximately 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of a dose of atorvastatin is excreted in urine following oral administration.

Special populations

Elderly

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 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.

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 4.2).

Haemodialysis

While studies have not been conducted in patients with end-stage renal disease, haemodialysis is not expected to markedly increase the clearance of atorvastatin since it is extensively bound to plasma proteins.

Hepatic insufficiency

Plasma concentrations of atorvastatin are significantly enhanced (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (See 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient

Inactive ingredients

The excipients are: anhydrous sodium carbonate, butylated hydroxyanisole, colloidal anhydrous silica, croscarmellose sodium, mannitol, microcrystalline cellulose, septifilm LP 010 (hypromellose, microcrystalline cellulose and stearic acid) and sodium lauryl sulphate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from moisture. Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

DEZZOLIP 10/20/40/80:

Pack size: 28 tablets or 30 tablets

Tablets are packed in Alu-Alu blister composed of silver opaque Alu-Alu cold form laminate & silver opaque Aluminium foil. Each blister strip contains 7 tablets or 10 tablets. Four blister strips of 7’s or three blister strips of 10’s are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

DEZZOLIP 10: 48/7.5/1202

DEZZOLIP 20: 48/7.5/1203

DEZZOLIP 40: 48/7.5/1204

DEZZOLIP 80: 48/7.5/1205

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 25 November 2016

10. DATE OF REVISION OF THE TEXT

June 2022