PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

PROPRIETARY NAME (and dosage form)

BEZALIP® Tablets

BEZALIP® RETARD Tablets

COMPOSITION:

BEZALIP® Tablets: Each tablet contains 200 mg bezafibrate.

Other ingredients are:

Kernel: Magnesium stearate, maize starch, microcrystalline cellulose, silica colloidal anhydrous, sodium starch glycollate, starch (pregelatinised).

Film coating: Opadry white II consisting of: macrogol, polyvinyl alcohol, titanium dioxide, talc.

BEZALIP® RETARD Tablets: Each tablet contains 400 mg bezafibrate.

Other ingredients are:

Kernel: Hypromellose, lactose monohydrate, magnesium stearate, povidone, silica colloidal anhydrous, sodium lauryl sulphate.

Film coating: Hypromellose, lactose monohydrate, macrogol, poly(ethylacrylate methylmethacrylate), polysorbate, sodium citrate, talc, titanium dioxide.

Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION:

A 7.5 Serum cholesterol reducers

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

Bezafibrate lowers elevated blood lipids (triglycerides and cholesterol). Bezafibrate also lowers LDL* and moderately raises HDL*** cholesterol. It also lowers VLDL**. The activity of the triglyceride lipases involved in this process (lipoprotein lipase in the blood and hepatic triglyceride lipase) is increased by bezafibrate. In the course of the intensified degradation of triglyceride-rich lipoproteins (chylomicrons, VLDL), precursors for the formation of HDL are formed, which may explain an increase in HDL. Furthermore, cholesterol biosynthesis is reduced by bezafibrate, which is accompanied by a stimulation of the LDL-receptor-mediated lipoprotein catabolism.

**VLDL: Very Low Density Lipoproteins which transport the endogenously formed triglycerides; precursors of LDL.
*LDL: Low Density Lipoproteins which represent the main transport fraction for cholesterol.
***HDL: High Density Lipoproteins.

They play a role in the degradation of triglyceride-rich lipoproteins (chylomicrons and VLDL) and in the removal of cholesterol from the endothelium cells of the arteries.

Bezafibrate also exerts an effect on thrombogenic factors: in addition to an inhibition of platelet aggregation, a significant decrease in elevated plasma fibrinogen levels, as well as a reduction of blood viscosity can be achieved. However, the clinical significance of this finding is not known. A reduction in blood glucose concentration due to an increase in glucose tolerance has been reported in diabetic patients with hyperlipidemia. In the same patients, the concentration of fasting and postprandial free fatty acids was reduced by bezafibrate.

Pharmacokinetic Properties:

Absorption:

Bezafibrate is rapidly and almost completely absorbed from the standard film coated tablet formulation. Bezafibrate 200 mg: A peak plasma concentration of about 8 mg/ℓ is reached after about 2 hours following a single 200 mg dose in healthy volunteers. Bezafibrate 400 mg Retard: A peak

concentration of about 6 mg/ℓ is reached after 3 to 4 hours. The relative bioavailability of bezafibrate Retard compared to the standard form is about 70 %.

Distribution:

94 to 96 % of bezafibrate is bound to protein in human serum, and the apparent volume of distribution is about 17 ℓ.

Metabolism and Elimination:

Elimination is rapid, with excretion almost exclusively renal. 95 % of the activity of the ^{14}C-labelled drug is recovered in the urine and 3 % in the faeces within 48 h. Fifty percent of the applied dose is recovered in the urine as unchanged drug and 20 % in form of glucuronides. The rate of renal clearance ranges from 3,4 to 6,0 ℓ/hour. The elimination half life of bezafibrate is 1 to 2 hours. The apparent half life of bezafibrate Retard is about 2 to 4 hours.

Pharmacokinetics in Special Populations:

Pharmacokinetic investigations in the elderly suggest that elimination may be delayed in cases of impaired liver function. Liver disease (except fatty liver) is a contraindication for the use of bezafibrate (refer to **CONTRAINDICATIONS)**. In elderly patients, there is a physiological reduction of the renal function with age. Bezafibrate dosage should be adjusted based on the serum creatinine and creatinine clearance values as indicated in the table under **Special Dosage Instructions**. Bezafibrate Retard should not be used in elderly as the creatinine clearance after 70 years of age is normally lower than 60 mℓ/min. The elimination of bezafibrate is reduced in patients with impaired renal function and dosage adjustments are necessary to prevent drug accumulation and toxic effects. There is a correlation between creatinine clearance and the elimination half life of bezafibrate; with decreasing creatinine clearance the elimination half life is increasing. Because of its high protein binding, bezafibrate cannot be dialysed (cuprophane filter).
The use of bezafibrate is contraindicated in dialysis patients.

INDICATIONS:

Primary hyperlipidaemia types IIa, IIb, III, IV and V (Fredrickson classification) corresponding to groups I, II and III of the European Atherosclerosis Society guidelines: when diet alone or improvements in lifestyle such as increased exercise or weight reduction do not lead to an adequate response. Secondary hyperlipidaemias, e.g. severe hypertriglyceridaemias, when sufficient improvement does not occur after correction of the underlying disorder (e.g. diabetes mellitus).

CONTRAINDICATIONS:

- BEZALIP tablets are contraindicated in patients who are hypersensitive to bezafibrate, or fibrates or other components of BEZALIP.
- BEZALIP is contraindicated in patients with liver dysfunction. BEZALIP may be beneficial for patients with fatty liver concomitant with hyperlipidaemia, but caution should be exercised.
- Gall-bladder diseases with or without cholelithiasis (as a possible liver involvement cannot be excluded).
- BEZALIP 200 mg is contraindicated in patients undergoing dialysis and with impaired renal function (serum creatinine > 530 µmol/ℓ or creatinine clearance < 15 mℓ/min). As BEZALIP is normally highly protein bound, it should not be given to patients with nephrotic syndrome.
- BEZALIP RETARD 400 mg is contraindicated in patients undergoing dialysis and with impaired renal function (serum creatinine > 135 µmol/ℓ or creatinine clearance < 60 mℓ/min).
- Combination therapy of BEZALIP with HMG-CoA reductase inhibitors in patients with predisposing factors for myopathy e.g. impaired renal function, severe infection, trauma, and surgery, disturbances of the hormonal or electrolyte balance.
- Known photoallergic or phototoxic reactions to fibrates.

WARNINGS AND SPECIAL PRECAUTIONS:

There is insufficient experience in children to recommend the use of BEZALIP in children.
Since oestrogens may lead to a rise in lipid levels the prescribing of BEZALIP in patients taking oestrogens or oestrogen containing contraceptives must be critically considered on an individual basis.

Due to the risk of rhabdomyolysis, BEZALIP should only be administered together with HMG-CoA reductase inhibitors in exceptional cases when strictly indicated. Patients receiving this combination therapy must be fully informed of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the first signs of myopathy. BEZALIP alters the composition of bile. There have been reports of the development of gallstones. Appropriate diagnostic procedures should be performed if cholelithiasis related signs and symptoms should occur (refer to **SIDE EFFECTS**).

Muscular weakness, myalgia and muscle cramps, often accompanied by a considerable increase in creatinine kinase (CK) may occur. In isolated cases, severe muscular damage (rhabdomyolysis) has been observed. In most cases, this syndrome resulted from overdosage of BEZALIP or from inappropriate usage of BEZALIP RETARD, most frequently in the presence of impaired renal function.

BEZALIP contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take BEZALIP.

INTERACTIONS:

When BEZALIP is used concurrently with cholestyramine, an interval of 2 hours should be maintained between taking the two medicaments, since the absorption of BEZALIP is impaired by cholestyramine.

BEZALIP may interact with oral coumarin anti-coagulants and the dosage of these agents may have to be reduced. Adjustments should be made by means of checks on the blood clotting status.
BEZALIP may potentiate the action of sulphonylureas and insulin.
MAO-inhibitors with hepatotoxic potential must not be administered together with BEZALIP.
Interaction between HMG-CoA reductase inhibitors (statins) and fibrates may vary in nature and intensity depending on the combination of the administered drugs. A pharmacodynamic interaction between these two classes of drugs may perhaps, in some cases, also contribute to an increased risk of myopathy.

In isolated cases, a pronounced though reversible, impairment of renal function (accompanied by a corresponding increase in the serum creatinine level) has been reported in organ transplant patients receiving immune suppressant therapy and concomitant BEZALIP.
Accordingly, renal function should be closely monitored in these patients and, in the event of relevant significant changes in laboratory parameters, BEZALIP should, if necessary, be discontinued.

HUMAN REPRODUCTION:

Due to lack of adequate clinical experience, BEZALIP is contraindicated during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

The basis of the treatment of all disorders of lipid metabolism is by weight loss, physical activity and adequate treatment of other metabolic disorders (e.g. diabetes, gout). This should be prescribed by the doctor. Obese patients should lose weight.

The dose is generally one BEZALIP 200 mg tablet taken 2 or 3 times daily as determined by the doctor. The tablet should be swallowed whole, with a little fluid, after the 3 main meals.
The standard dosage for BEZALIP RETARD 400 mg is 1 tablet once daily. The tablet should be taken in the morning or evening with or after meals. The tablets should be swallowed whole with sufficient fluid.

In patients with sensitive stomachs, the dose may be started slowly. Start with 1 tablet daily, adding the second tablet after 3 to 4 days and the third after a further 3 to 4 days.
The dosage in patients with renal insufficiency must be adjusted according to serum creatinine levels.
Treatment with BEZALIP should be monitored over the first 8 weeks of treatment by the determination of the triglyceride, total cholesterol and HDL-cholesterol levels at least three times. If no significant reduction of triglyceride and total cholesterol is obtained, treatment should be discontinued.

Special Dosage Instructions:

For patients with a history of gastric sensitivity, the dosage may be gradually increased to the maintenance level. The dosage in patients with impaired renal function must be adjusted according to serum creatinine levels or creatinine clearance. Due to the necessary dosage reduction in case of impaired renal function (serum creatinine > 135 µmol/ℓ or creatinine clearance < 60 mℓ/min), BEZALIP RETARD should be replaced by BEZALIP 200 mg tablets and dosed appropriately.

Serum creatinine	**Creatinine clearance**	**Dosage 200 mg**	**Dosage 400 mg**
Up to 135 µmol/ℓ	Over 60 mℓ/min	1 tablet 3 times daily	1 tablet daily
136 – 225 µmol/ℓ	60 – 40 mℓ/min	1 tablet 2 times daily	Contraindicated
226 – 530 µmol/ℓ	40 – 15 mℓ/min	1 tablet every day or second day	Contraindicated
Over 530 µmol/ℓ	Less than 15 mℓ/min	Contraindicated	Contraindicated

It should be taken into account that creatinine clearance is a more reliable parameter than serum creatinine (especially in the elderly). The creatinine clearance can be estimated using the following equation (Cockroft and Gault equation) which is applicable to adults only:

Men:

Cl_{Cr} (mℓ/min) = $\frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{C_{Cr}\ (\mu\text{mol}/\ell)} \times 1{,}23$

Cl_{Cr} = creatinine clearance

C_{Cr} = serum creatinine

For women, the value should be reduced to 85 % of that estimated by this equation.

In elderly patients, there is a physiological reduction of the renal function with age. BEZALIP dosage should be adjusted based on the serum creatinine and creatinine clearance values as indicated in the above table. BEZALIP RETARD should not be used in the elderly as the creatinine clearance after 70 years of age is normally lower than 60 mℓ/min.

SIDE EFFECTS:

A total of 3 581 patients were enrolled into 48 clinical studies. Side effects observed during the clinical development and subsequent use in clinical practice consisted mainly of symptoms of gastro intestinal disturbances which were usually transient and rarely led to discontinuation of the medicine. Myopathy (rhabdomyolysis) was mostly observed when dose reduction was not implemented in patients with impaired renal function. None of the side effects could be considered to affect long term safety, as they usually occurred within the first few months of therapy and were either transient or disappeared upon withdrawal of the medicine.

The frequency of adverse drug reactions (ADRs) according to MedDRA System Organ Class is displayed in the table below:

MedDRA System Organ Class	**Very rare: (</10 000)**	**Uncommon: (>1/1 000 and <1/100)**	**Common**
Blood and the Lymphatic System Disorders	Pancytopenia Thrombocytopenia		
Immune System Disorders		Hypersensitivity reactions	
Metabolism and Nutrition Disorders			Decreased appetite
Nervous System Disorders		Dizziness Headache	
Gastrointestinal Disorders		Abdominal distension Nausea	
Hepatobiliary Disorders	Cholelithiasis	Cholestasis	
Skin and Subcutaneous Tissue Disorders	Thrombocytopenic purpura Erythema multiforme	Pruritis Urticaria Photosensitivity	

	Stevens-Johnson syndrome Toxic epidermal necrolysis	reaction Alopecia	
Musculoskeletal, Connective Tissue and Bone Disorders	Rhabdomyolysis	Muscular weakness Myalgia Muscle cramp	
Renal and Urinary Disorders		Acute renal failure	
Reproductive Systems and Breast Disorders		Erectile dysfunction	
Investigations	Haemoglobin decreased Platelet increased White blood cell count decreased Gamma-glutamyl transferase increased Transaminase increased	Increased blood creatinine phosphokinase Blood creatinine increased Blood alkaline phosphatase increased	

Laboratory abnormalities:

The following laboratory abnormalities have been observed during clinical trials and also reported during post marketing period:

- Increased blood creatinine phosphokinase (uncommon)
- Increased platelets (uncommon)
- Decreased haemoglobin (uncommon)
- Decreased haematocrit (uncommon)
- Decreased white blood cells (uncommon)

- Increased transaminase (uncommon)
- Decreased alkaline phosphatase (uncommon).

Decreased gamma-glutamyl transferase (uncommon) and in parallel alkaline phosphatase could be used as an indicator of patient compliance.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Specific clinical picture of BEZALIP intoxication (apart from rhabdomyolysis) is unknown. Thus, appropriate symptomatic therapy as necessary in case of overdose. There is no specific antidote. In cases of rhabdomyolysis (mostly in patients with impaired renal function), administration of BEZALIP/BEZALIP RETARD must be stopped immediately and renal function must be carefully monitored.

IDENTIFICATION:

BEZALIP tablets: White, round, film coated tablet marked G6 on one face.

BEZALIP RETARD tablets: White, round, film coated tablet marked D9 on one face.

PRESENTATION:

BEZALIP tablets: Packs with 90 tablets.

BEZALIP RETARD tablets: Packs with 30 tablets.

STORAGE INSTRUCTIONS:

BEZALIP and BEZALIP RETARD tablets can be stored under normal conditions at or below 25 °C.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

BEZALIP: Q/7.5/104

BEZALIP RETARD: S/7.5/270

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Date of registration: 13 January 1984

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