NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Bezalip, 200 mg film coated tablets
Bezalip Retard, 400 mg sustained release, film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 200 mg of bezafibrate.

Each sustained release, film coated tablets contains 400 mg of bezafibrate.

Excipient with known effect: lactose monohydrate (Bezalip Retard)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Bezalip is a white, round film-coated tablet imprinted with 'G6' at reverse.

Bezalip Retard is a white, round film-coated tablet engraved D9 on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bezalip and Bezalip is indicated for:

- 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 hypertriglyceridemias, when sufficient improvement does not occur after correction of the underlying disorder (e.g. diabetes mellitus).

4.2 Dose and method of administration

Adults

The standard dosage for Bezalip 200 mg tablets is 1 tablet (200 mg) 3 times daily. In cases of good therapeutic response, especially in hypertriglyceridaemia, the dosage can be reduced to 1 tablet twice daily. For patients with a history of gastric sensitivity, the dosage may be gradually increased to the maintenance level.

The standard dosage for Bezalip Retard 400 mg tablets is 1 tablet once daily.

Special populations

Patient with renal Impairment

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 >1.5 mg/100 ml, i.e. > 135 micromol/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 (Bezalip 200 mg)*	*Dosage (Bezalip Retard 400 mg)*
Up to 1.5 mg/100 ml (Up to 135 micromol/l)	Over 60 ml/min	3 film coated tablets/day (1 tablet 3 times daily)	1 Retard tablet/day
1.6 – 2.5 mg/100 ml (136 – 225 micromol/l)	60 – 40 ml/min	2 film coated tablets/day (1 tablet twice daily)	Contraindicated
2.6 – 6 mg/100 ml (226 – 530 micromol/l)	40 – 15 ml/min	1 film coated tablet every 1 or 2 days	Contraindicated
Over 6 mg/100 ml (Over 530 micromol/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:

$$\text{Men: } Cl_{Cr} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{72 \times C_{Cr}\ (\text{mg/dl})}\ (\text{ml/min})$$

Cl_{Cr} = creatinine clearance

C_{Cr} = serum creatinine

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

In dialysis patients, the use of Bezalip and Bezalip Retard is contraindicated. Bezafibrate dosage should be carefully adjusted based on the renal function and a careful evaluation of the benefit/risk ratio. To avoid overdosage (and thus e.g. rhabdomyolysis) regular measurement of bezafibrate plasma concentrations are advisable.

Elderly
In elderly patients, there is a physiological reduction of the renal function with increasing age. Bezafibrate dosage should be adjusted according to the serum creatinine and creatinine clearance values as indicated in the above table.

Bezalip Retard should not be used in elderly patients, as the creatinine clearance after 70 years of age is normally lower than 60 ml/min.

Paediatric population
Indications for the use of bezafibrate in children must be particularly carefully considered. A definite dosage recommendation cannot be given.

Duration of treatment
Treatment with Bezalip/Bezalip Retard is normally a long term therapy.

Method of administration
Bezalip 200 mg tablets

The film coated tablet should be swallowed whole with sufficient fluid, with or after meals.

Bezalip Retard 400 mg sustained release tablets

The sustained release film coated tablet should be taken in the morning or evening with or after meals. The tablet should be swallowed whole with sufficient fluid.

4.3 Contraindications

Bezafibrate must not be used in:

- liver disease (with the exception of fatty liver which is a frequent accompaniment to hypertriglyceridaemia)
- gall-bladder diseases with or without cholelithiasis (as a possible liver involvement cannot be excluded)
- Bezalip 200 mg: Patients with severe renal impairment presenting serum creatinine levels > 6 mg / 100 ml (> 530 micromol/l) or creatinine clearance < 15 ml / min and all patients undergoing dialysis
- Bezalip Retard 400 mg: in patients with renal impairment presenting serum creatinine levels > 1.5 mg/100ml (>135 micromol/l) or creatinine clearance < 60 ml/min and all patients undergoing dialysis
- known hypersensitivity to bezafibrate, to any component of the product or to other fibrates
- known photoallergic or phototoxic reactions to fibrates
- during pregnancy and lactation (see Fertility, pregnancy and lactation)
- combination therapy of Bezalip 200 mg and Bezalip Retard 400 mg with HMG-CoA reductase inhibitors in patients with predisposing factors for myopathy e.g. pre-existing renal impairment, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance.
- elderly patients, as the creatinine clearance after 70 years of age is normally lower than 60 ml/min.

4.4 Special warnings and precautions for use

Compliance with diet and other measures which improve lipid disorders such as physical activity, weight loss and adequate treatment of other metabolic disorders (e.g. diabetes, gout) is of the utmost importance.

The patient's response to therapy should be monitored at regular intervals and treatment should be terminated if an adequate response has not been achieved within 3 to 4 months.

Since oestrogens may lead to a rise in lipid levels, the prescribing of Bezalip/Bezalip Retard in patients taking oestrogens or oestrogen-containing contraceptives must be critically considered on an individual basis.

In patients with hypoalbuminaemia, e.g. nephrotic syndrome, and in patients with impaired renal function, Bezalip Retard should be replaced by Bezalip in reduced dosage and renal function should be monitored regularly. In patients with existing-renal impairment, acute renal failure may develop if dosage recommendations according to the presenting serum creatinine or creatinine clearance are not strictly followed.

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

Due to the risk of rhabdomyolysis, Bezalip/Bezalip Retard should only be administered together with HMG-CoA reductase inhibitors in exceptional cases when strictly indicated. Patients receiving this combination therapy must be informed carefully of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the first signs of myopathy. This combination therapy must not be used in patients with predisposing factors for myopathy (impaired renal function, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance).

Bezalip/Bezalip Retard alters the composition of bile. There have been isolated reports of the development of gallstones. It is not certain whether the occurrence of gallstones is increased as a

result of long-term treatment with Bezalip/Bezalip Retard, as has been observed with other medicines with a similar mechanism of action, or whether pre-existing gallstones increase in size in the course of Bezalip/Bezalip Retard therapy.

Since cholelithiasis as a possible side effect of Bezalip therapy cannot be excluded, appropriate diagnostic procedures should be performed if cholelithiasis-related signs and symptoms should occur (see Undesirable Effects).

When Bezalip is given in combination with anion-exchange resins (e.g. cholestyramine), the two medicines should be taken at least 2 hours apart.

Paediatric population

Indications for the use of Bezalip in children must be particularly carefully considered. A definite dosage recommendation for children cannot be given.

4.5 Interaction with other medicines and other forms of interaction

When Bezalip or Bezalip Retard is used at the same time as other medicines or substances the following interactions must be taken into account:

Bezalip and Bezalip Retard may enhance the action of anticoagulants of the coumarin type. For this reason, the dose of the anticoagulant should be reduced by 30 - 50% at the start of treatment with Bezalip or Bezalip Retard and then titrated according to the blood clotting parameters.

The action of sulphonylureas and insulin may be enhanced by Bezalip or Bezalip Retard. This may be due to an improved glucose utilization with simultaneous reduction in insulin requirement.

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 immuno-suppressant therapy and concomitant bezafibrate. Accordingly, renal function should be closely monitored in these patients and, in the event of relevant significant changes in laboratory parameters, bezafibrate should, if necessary, be discontinued.

When Bezalip or Bezalip Retard is used concurrently with anion-exchange resins (e.g. cholestryramine), an interval of at least 2 hours should be maintained between the two medicines, since the absorption of bezafibrate is impaired.

Perhexiline hydrogen maleate or MAO-inhibitors (with hepatotoxic potential) must not be administered together with Bezalip or Bezalip Retard.

Interaction between fibrates and HMG-CoA reductase inhibitors (statins) may vary in nature and intensity depending on the combination of the administered medicines. A pharmacodynamic interaction between these two classes of medicines may in some cases, also contribute to an increased risk of myopathy (rhabdomyolysis).

4.6 Fertility, pregnancy and lactation

Due to lack of adequate experience, Bezalip and Bezalip Retard are contraindicated during pregnancy and lactation (see Contraindications).

4.7 Effects on ability to drive and use machines

No information available.

4.8 Undesirable effects

The overall safety profile of bezafibrate is based on a combination of clinical data and post-marketing experience.

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 bezafibrate. Myopathy (rhabdomyolysis) was mostly observed when dose reduction was not implemented in patients with renal impairment. 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 bezafibrate.

The frequency of adverse drug reactions (ADRs) according to MedDRA System Organ Class is displayed in the table below. Frequency of reporting: Common (>1/100 and <1/10), Uncommon (≥1/1,000 and <1/100), Rare (>1/10,000 and <1/1000), Very rare (<1/10,000).

MedDRA System Organ Class **Frequency: Adverse Events**	
Blood and Lymphatic System	
Very rare:	Pancytopenia
	Thrombocytopenia
Immune System	
Uncommon:	Hypersensitivity reactions including anaphylactic reactions.
Metabolism and Nutrition System	
Common:	Decreased appetite
Nervous System	
Uncommon:	Dizziness
	Headache
Rare:	Neuropathy peripheral
	Paraesthesia
Gastrointestinal Disorders	
Common:	Gastrointestinal disorder
Uncommon:	Abdominal distension
	Abdominal pain
	Constipation
	Diarrhoea
	Dyspepsia
	Nausea
Rare:	Pancreatitis
Hepatobiliary Disorders	
Uncommon:	Cholestasis
Very rare:	Cholelithiasis (see Special warnings and precautions for use)
Skin and Appendages Disorders	
Uncommon:	Pruritus
	Urticaria
	Photosensitivity reaction
	Alopecia
	Rash
Very rare:	Thrombocytopenic purpura
	Erythema multiforme
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
Uncommon:	Muscular weakness
	Myalgia
	Muscle cramp
Very rare:	Rhabdomyolysis
Renal and Urinary Disorders	
Uncommon:	Acute renal failure
Reproductive System and Breast Disorders	
Uncommon:	Erectile dysfunction NOS

MedDRA System Organ Class Frequency: Adverse Events	
Respiratory, thoracic and mediastinal disorders	
Very rare:	Interstitial lung disease
Psychiatric disorders:	
Rare:	Depression, insomnia, memory loss
Investigations	
Uncommon:	Increased blood creatinine phosphokinase
	Blood creatinine increased
	Blood alkaline phosphatase increased
Very rare:	Haemoglobin decreased
	Platelet increased
	White blood cell count decreased
	Gamma-glutamyl transferase increased
	Transaminase increased

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

Uncommon: Increased blood creatinine phosphokinase, increased platelets, decreased haemoglobin, decreased haematocrit, decreased white blood cells, increased transaminase, decreased alkaline phosphatase, decreased gamma-glutamyl transferase and in parallel alkaline phosphatase could be used as an indicator of patient compliance.

4.9 Overdose
As the specific clinical picture of intoxication is unknown, symptomatic therapy should be used as necessary. There is no specific antidote.

In cases of rhabdomyolysis (mostly in patients with impaired renal function), administration of Bezalip or Bezalip Retard must be stopped immediately and renal function must be carefully monitored.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Lipid modifying agents, plain; fibrates, ATC code: C10AB02

Bezafibrate lowers elevated blood lipids (triglycerides and cholesterol). Elevated VLDL and LDL are reduced by treatment with bezafibrate, whilst HDL-levels are increased. The activity of triglyceride lipases (lipoprotein lipase and hepatic lipoproteinlipase) involved in the catabolism of triglyceride-rich lipoproteins 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 explains an increase in HDL. Furthermore, cholesterol biosynthesis is reduced by bezafibrate, which is accompanied by a stimulation of the LDL-receptor-mediated lipoprotein catabolism.

Elevated fibrinogen appears to be an important risk-factor, alongside the lipids, smoking and hypertension, in the development of atheroma. Fibrinogen plays an important role in viscosity, and therefore blood flow, and also appears to play an important role in thrombus development and lysability.

Bezafibrate exerts an effect on thrombogenic factors. A significant decrease in elevated plasma fibrinogen levels can be achieved. This may lead, amongst other things, to a reduction in both blood and plasma viscosity. Inhibition of platelet aggregation has also been observed.

A reduction in blood glucose concentration due to an increase in glucose tolerance has been reported in diabetic patients. In the same patients, the concentration of fasting and postprandial free fatty acids was reduced by bezafibrate.

5.2 Pharmacokinetic properties

Absorption

Bezafibrate is rapidly and almost completely absorbed from the standard film-coated tablet formulation. A peak plasma concentration of about 8 mg/l is reached after 1-2 hours following a single 200 mg dose in healthy volunteers.

With 400 mg bezafibrate sustained release tablets, a peak concentration of about 6 mg/l is reached after 3-4 hours.

Distribution

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

Metabolism and elimination

Elimination is rapid, with excretion almost exclusively renal. 95% of the activity of the ^{14}C-labelled substance is recovered in the urine and 3% in the feces within 48 hours. 50% of the applied dose is recovered in the urine as unchanged substance 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 1-2 hours. The half-life of bezafibrate sustained release tablets is about 2-4 hours.

The elimination of bezafibrate is reduced in patients with impaired renal function and dosage adjustments are necessary to prevent accumulation and toxic effects.

There is a correlation between creatinine clearance and the elimination half-life of bezafibrate; with decreasing clearance the elimination half-life is increasing.

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.

Dialysis behaviour

Bezafibrate cannot be dialysed (cuprophane filter). Bezafibrate Retard is contraindicated in dialysis patients.

Bioavailability

Bezalip is almost completely absorbed after oral administration. The relative bioavailability of bezafibrate retard compared to the standard form is about 70%.

Special Populations

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 in the Dose and method of administration section. Bezalip Retard should not be used in elderly as the creatinine clearance after 70 years of age is normally lower than 60 ml/min.

Due to its high protein binding, bezafibrate cannot be dialysed (cuprophane filter). In all patients undergoing dialysis, the use of Bezalip and Bezalip Retard is contraindicated.

5.3 Preclinical safety data
None.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Bezalip: Colloidal silicon dioxide, maize starch, starch pregelatinised microcrystalline cellulose, sodium starch glycollate, magnesium stearate and film coat (Opadry White II).

Bezalip Retard: Lactose, polyvidone K 25, sodium lauryl sulphate, hypromellose, colloidal silicon dioxide, magnesium stearate and film coat (poly(ethylacrylate, methylmethacrylate), polysorbate 80, hypromellose, macrogol 10 000, lactose, talc, titanium dioxide, sodium citrate (dihydrate)).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
60 months

6.4 Special precautions for storage
Store below 30^{o}C.

6.5 Nature and contents of container
PVC/Aluminium foil blister strips.

Pack sizes of 10 and 30 tablets (Bezalip Retard) and 90 tablets (Bezalip).

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL
18 April 1984 (Bezalip)
9 November 1989 (Bezalip Retard)

10. DATE OF REVISION OF THE TEXT
21 February 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format
8.	Sponsor company name and address details updated