PROFESSIONAL INFORMATION

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

Sandoz® Bezafibrate 400 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Sandoz Bezafibrate 400 tablet contains 400 mg bezafibrate.

Contains sugar (lactose 62,00 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round, biconvex, film-coated tablets.

4. CLINICAL PARTICULARS

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

Frederickson defines the following six types of hyperlipoproteinaemias:

Fredrickson's classification:

Type I	Chylomicrons	present;		
Type IIa	LDL	raised;		
Type IIb	LDL	raised;	VLDL	raised;
Type III	IDL	raised;		
Type IV	VLDL	raised;		
Type V	Chylomicrons	present;	VLDL	raised

4.2 Posology and method of administration

Posology

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 standard dosage for SANDOZ BEZAFIBRATE 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.

The dosage in patients with renal insufficiency must be adjusted according to serum creatinine levels.

Treatment with SANDOZ BEZAFIBRATE 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 instruction

Serum creatinine	Creatinine clearance	Dosage 400 mg
Up to 135 µmol/L	Over 60 ml/min	1 tablet daily
136-225 µmol/L	60-40 ml/min	Contraindicated
226-530 µmol/L	40-15 ml/min	Contraindicated
Over 530 µmol/L	Less than 15 ml/min	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)= $\frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times 1,23}{C_{cr}\ (\mu mol/L)}$

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.

SANDOZ BEZAFIBRATE should not be used in the elderly as the creatinine clearance after 70 year of age is normally lower than 60 ml/min.

4.3 Contraindications

- Known hypersensitivity to bezafibrate, to any component of the product (see section 6.1) or to other fibrates.
- Pregnancy and lactation.
- SANDOZ BEZAFIBRATE is contraindicated in patients with liver dysfunction.
- SANDOZ BEZAFIBRATE may be beneficial for patients with fatty liver concomitant

with hyperlipidaemia, but caution should be exercised.

- Gall bladder disease with or without cholelithiasis (as a possible liver involvement cannot be excluded).
- Sandoz Bezafibrate 400 mg is contraindicated in patients undergoing dialysis and with impaired renal function (serum creatinine >135 µmol/L or creatinine clearance < 60 ml/min).
- Known photoallergic or phototoxic reactions to fibrates.
- Combination therapy of SANDOZ BEZAFIBRATE with HMG-CoA reductase inhibitors (statins) in patients with predisposing factors for myopathy (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

At the beginning of SANDOZ BEZAFIBRATE therapy, there may be a transient rise in the lipogenic index. The associated elevated excretion of cholesterol is a manifestation of mobilisation and elimination of cholesterol from the body**.**

SANDOZ BEZAFIBRATE should be used as an adjunct to diet and measures such as physical activity, weight loss and adequate treatment of other metabolic disorders (e.g. diabetes, gout).

Secondary causes of dyslipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease, pharmacological treatment, alcoholism should be adequately treated before Bezafibrate therapy is initiated.

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

Muscles

SANDOZ BEZAFIBRATE and other fibrates may cause myopathy, manifested as muscle weakness or pain, often accompanied by a considerable increase in creatine kinase (CPK). In isolated cases severe muscle damage (rhabdomyolysis) has been observed. The risk of rhabdomyolysis may be increased when higher than recommended doses of SANDOZ BEZAFIBRATE are used, most frequently in the presence of impaired renal function and in patients with predisposing factors for myopathy (including renal impairment, elderly (aged > 65 years), personal or family history of hereditary muscular disorders, previous history of muscular toxicity with a fibrate or other lipid lowering medicines, hypothyroidism, severe infection, trauma, surgery, disturbances of hormone or electrolyte imbalance and a high alcohol intake).

SANDOZ BEZAFIBRATE should be used with caution in combination with HMG-CoA reductase inhibitors as the combination of HMG-CoA inhibitors and fibrates has been shown to increase the incidence and severity of myopathy. Patients should be informed of symptoms and monitored for signs of myopathy and increased CPK activity and combination therapy discontinued if signs of myopathy develop. Combination therapy should not be used in patients with predisposing factors for myopathy (see section 4.3 and 4.5).

Gallstones

SANDOZ BEZAFIBRATE alters the composition of bile. There have been isolated reports of the development of gallstones.

As SANDOZ BEZAFIBRATE could cause cholelithiasis, appropriate diagnostic procedures should be performed if cholelithic symptoms and signs occur (see section 4.8).
When SANDOZ BEZAFIBRATE is given in combination with anion-exchange resins (e.g. cholestyramine), the two medicines should be taken at least two hours apart.

Precautions relating to excipients

SANDOZ BEZAFIBRATE contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take SANDOZ BEZAFIBRATE.
SANDOZ BEZAFIBRATE contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Interaction between HMG CoA-reductase inhibitors and fibrates 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 increase in the risk of myopathy (see sections 4.3 and 4.4). For specific dose recommendations of statins refer also to the Professional Information of the relevant product.

SANDOZ BEZAFIBRATE must not be taken concomitantly with monoamine oxidase (MAO) inhibitors with hepatotoxic potential.

Should combined therapy with an ion-exchange resin be considered necessary, there should be an interval of 2 hours between the intake of the resin and SANDOZ BEZAFIBRATE as the absorption of SANDOZ BEZAFIBRATE otherwise may be impaired.

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

Care is required in administering SANDOZ BEZAFIBRATE tablets to patients taking coumarin-type anti-coagulants, the action of which may be potentiated. The dosage of anti-coagulant should be reduced by up to 50 % and readjusted by monitoring blood coagulation.

As SANDOZ BEZAFIBRATE improves glucose utilisation the action of antidiabetic medication, including insulin, may be potentiated. Hypoglycaemia has not been observed although increased monitoring of the glycaemic status may be warranted for a brief period after introduction of SANDOZ BEZAFIBRATE.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of SANDOZ BEZAFIBRATE in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. SANDOZ BEZAFIBRATE is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation

No information is available about the excretion of SANDOZ BEZAFIBRATE into mother's milk (see section 4.3).

4.7 Effects on ability to drive and use machines

SANDOZ BEZAFIBRATE has been shown to cause dizziness and can have a minor to moderate effect on the ability to drive or use machines.

Patients should not drive or use machines if they are affected.

4.8 Undesirable effects

The frequency of adverse drug reaction (ADRs) according to MedDRA System Organ Class is displayed below.

Blood and lymphatic system disorders

Less frequent: Pancytopenia, thrombocytopenic purpura, anaemia, leucopenia.

Immune system disorders

Less frequent: Hypersensitivity reactions including anaphylactic reactions.

Metabolism and nutrition disorder

Frequent: Decreased appetite.

Less frequent: Mass gain.

Psychiatric disorders

Less frequent: Depression, insomnia.

Nervous system disorders

Less frequent: Dizziness, headache, fatigue or drowsiness, peripheral neuropathy, paraesthesia.

Respiratory, thoracic and mediastinal disorders

Less frequent: Interstitial lung disease.

Gastrointestinal disorders

Frequent: Gastrointestinal disorders.

Less frequent: Abdominal pain, constipation, dyspepsia, abdominal distension, diarrhoea, nausea.

Frequency unknown: Vomiting, pancreatitis.

Hepatobiliary disorders

Less frequent: Cholestasis, cholelithiasis (see section 4.4) slight abnormalities of liver function tests and hepatomegaly, apparently not indicative of hepatotoxicity.

Skin and subcutaneous tissue disorders

Less frequent: Pruritus, urticaria, photosensitivity reaction, alopecia, rash, erythema multiforme, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN).

Musculoskeletal and connective tissue disorders

Less frequent: Muscle weakness, myalgia, muscle cramp, rhabdomyolysis (see section 4.4).

Renal and urinary disorders

Less frequent: Acute renal failure.

Reproductive system and breast disorders

Less frequent: Erectile dysfunction NOS.

Investigations

Less frequent: Increased blood creatinine phosphokinase, blood creatinine increased, decreased gamma-glutamyl transferase and in parallel alkaline phosphatase, haemoglobin decreased, haematocrit decreased, platelet increased, white blood cell count decreased, gamma-glutamyl transferase increased, transaminase increased.

An increased incidence of cholecystitis, gallstones, and less frequently certain cardiovascular disorders, including cardiac arrhythmias have been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

No specific effects of acute overdose are known (apart from rhabdomyolysis), gastric pain, nausea and vomiting.

There is no specific antidote. Thus, appropriate symptomatic therapy is recommended in case of overdose. In cases of rhabdomyolysis SANDOZ BEZAFIBRATE must be stopped immediately and renal function carefully monitored.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 7.5 Serum-cholesterol reducers

ATC code: C10AB02

5.1 Pharmacodynamic properties

Mechanism of action

Bezafibrate is a fibric acid derivative. 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 the triglyceride lipases (lipoprotein lipase and hepatic lipoprotein lipase) 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.

Studies have shown bezafibrate to be effective in treating hyperlipidaemia in patients with diabetes mellitus. Some cases showed a beneficial reduction in fasting blood glucose.

Significant reductions in serum fibrinogen levels have been observed in hyperfibrinogenaemic patients treated with bezafibrate.

There is evidence that treatment with fibrates may reduce coronary heart disease events, but they have not been shown to decrease all-cause mortality in the primary or secondary prevention of cardiovascular disease.

5.2 Pharmacokinetic properties

Absorption

Bezafibrate is rapidly and almost completely absorbed from the standard tablet formulation. With SANDOZ BEZAFIBRATE, a peak concentration of about 8 mg is reached after about 4 hours.

Distribution

The protein-binding of bezafibrate in serum is approximately 95 %. The apparent volume of distribution is 17 L.

Biotransformation

50 % of the administered bezafibrate dose is recovered in the urine as unchanged active substance and 20 % in the form of glucuronides.

Elimination

Elimination is rapid with excretion almost exclusively renally. Ninety-five percent (95 %) of the activity of ^{14}C-labelled active substance is recovered in the urine and three percent (3 %) in the faeces within 48 hours. Fifty percent (50 %) of the applied dose is recovered in the urine as unchanged active substance and twenty percent (20 %) in form of glucuronides. The rate of renal clearance ranges from 3,4 to 6,0 l/h.

Pharmacokinetics in special populations

Patients with impaired renal function

The elimination of bezafibrate is reduced in patients with impaired renal function and dose adjustments may be necessary to prevent active substance accumulation and toxic effects (see section 4.2).

Patients with impaired hepatic function

Pharmacokinetic studies in the older people suggest that elimination may be delayed in cases of impaired liver function. Significant liver disease (except fatty liver) is a contraindication for the use of bezafibrate (see section 4.3).

Older patients

In older people, there is a physiological reduction of the renal function with age. Bezafibrate dose should be adjusted based on the serum creatinine and creatinine clearance values (see section 4.2).

Dialysability

Because of its high protein binding, bezafibrate cannot be dialysed (cuprophane filter). The use of bezafibrate is contraindicated in dialysis patients.

5.3 Preclinical safety data

The chronic administration of a high dose of bezafibrate to rats was associated with hepatic tumour formation. The dose was in the order of 30 to 40 times the human dose. No such effect was apparent at reduced intake levels approximating more closely to the lipid-lowering dose in human.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide (Aerosil 200), lactose, magnesium stearate, maize starch, opadry II white (OY-B-28920) (lecithin, polyvinyl alcohol, purified talc, titanium dioxide (CI 77891), xanthan gum), povidone K30 and purified talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 25 °C in a well closed container, protected from light.

6.5 Nature and contents of container

Amber glass bottles, clear PVC, Silver aluminium blisters, clear PVC/PE/PVDC Silver aluminium laminated foil blisters, sealed aluminium bags or white opaque securitainers of 30 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

29/7.5/0435

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 September 1996

10. DATE OF REVISION OF THE TEXT

04 November 2022

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Sandoz Bezafibrate 400	S2	BOT0200498
Namibia	Sandoz Bezafibrate 400	NS2	04/7.5/1464

ATC Code: C10AB02 – Fibrates

Name and address of manufacturer:

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