SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fibrazate® XL 400 mg Modified Release Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of bezafibrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release tablet.

White, round, film-coated, biconvex tablet, debossed with '400' on one side, and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fibrazate® XL 400 mg Modified Release Tablets are indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:

- Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.
- Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.

4.2 Posology and method of administration

Posology

Adults

The recommended daily dose for Fibrazate® XL 400mg Tablets is one tablet, equivalent to 400mg bezafibrate, after a meal either in the morning or at night.

Older people

Fibrazate® XL 400mg Tablets should not be prescribed/administered to older people whose creatinine clearance is below 60ml/min (see Renal impairment below).

Paediatric population
Information available to date is not adequate for a dose recommendation in children.

Renal impairment
Fibrazate® XL 400mg Tablets are contraindicated in dialysis patients.

Bezafibrate should not be given to patients with renal impairment with serum creatinine
> 135 micromol/l or creatinine clearance < 60 ml/min. Such patients may be treated with conventional tablets using an appropriately reduced daily dose.

For patients with a history of gastric sensitivity, the dosage may be gradually increased over 5-7 days to the maintenance level.

The response to therapy is normally rapid, although a progressive improvement may occur over a number of weeks. Treatment should be withdrawn if an adequate response has not been achieved within 3 to 4 months.

Method of administration
Swallow whole tablet with sufficient fluid.

4.3 Contraindications

- Significant hepatic disease (other than fatty infiltration of the liver associated with raised triglyceride values).
- Gall bladder disease with or without cholelithiasis.
- Patients with nephrotic syndrome and severe renal impairment (serum creatinine > 135 micromol/l or creatinine clearance < 60ml/min.) and patients undergoing dialysis.
- Concomitant use of HMG CoA reductase inhibitors (statins) in patients with predisposing factors for myopathy (see sections 4.4 and 4.5).
- Hypersensitivity to bezafibrate or any component of the product or to other fibrates.
- Known photoallergic or phototoxic reactions to fibrates.

4.4 Special warnings and precautions for use

- 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, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism should be adequately treated before Bezafibrate therapy is initiated.

- 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 bezafibrate are used, most frequently in the presence of impaired renal function and in patients with predisposing factors for myopathy, (including renal impairment, older (aged >65 years), personal of familial history of hereditary muscular disorders and previous history of muscular toxicity with a fibrate or other lipid lowering drugs, hypothyroidism, severe infection, trauma, surgery, disturbances of hormone or electrolyte imbalance and a high alcohol intake).

- 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).

- Bezafibrate alters the composition of bile. There have been isolated reports of the development of gallstones.

- As bezafibrate could cause cholelithiasis appropriate diagnostic procedures should be performed if cholelithic symptoms and signs occur (see section 4.8).

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Care is required in administering Fibrazate® XL 400mg 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 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 Fibrazate® XL 400mg Tablets

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 Fibrazate® XL 400mg Tablets as the absorption of 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 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.

MAO-inhibitors (with hepatotoxic potential) should not be administered together with bezafibrate.

Interaction between HMG CoA reductase inhibitors 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, in some cases, also contribute to an increase in the risk of myopathy (see section 4.3 and 4.4) for specific dose recommendations of statins refer also to the SPC of the relevant product.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of bezafibrate in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Fibrazate® XL 400mg Tablets are not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

There is insufficient information on the excretion of bezafibrate or its metabolites in human breast milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fibrazate® XL 400mg Tablets therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Fibrazate® XL 400mg Tablets have been shown to cause dizziness and can have a minor to moderate effect on the ability to drive or operate machinery. Patients should not drive or use machines if affected.

4.8 Undesirable effects

The overall safety profile of bezafibrate is based on a combination of clinical study data and post-marketing experience.
The frequency of adverse drug reactions (ADRs) according to MedDRA System Organ Class is displayed below.
Frequency of reporting: Common (≥ 1/100 to <1/10), Uncommon (≥ 1/1,000 to <1/100), Rare (≥ 1/10,000 to <1/1000), Very rare (<1/10,000).

Blood and lymphatic system disorders:
Very rare: Pancytopenia, thrombocytopenic purpura.

Immune system disorders:
Uncommon: Hypersensitivity reactions including anaphylactic reactions.

Metabolism and nutrition disorders:
Common: Decreased appetite.

Nervous system disorders:
Uncommon: Dizziness, headache.
Rare: Peripheral neuropathy, paraesthesia.

Psychiatric disorders:
Rare: Depression, insomnia.

Gastrointestinal disorders:
Common: Gastrointestinal disorders.
Uncommon: Abdominal pain, constipation, dyspepsia, abdominal distension, diarrhoea, nausea.
Rare: Pancreatitis

Hepatobiliary disorders:
Uncommon: Cholestasis.
Very rare: Cholelithiasis.

Skin and subcutaneous tissue disorders:
Uncommon: Pruritus, urticaria, photosensitivity reaction, alopecia, rash.
Very rare: 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.

Respiratory, thoracic and mediastinal disorders:
Very rare: Interstitial lung disease.

Investigations:
Uncommon: Increased blood creatinine phosphokinase, blood creatinine increased, decreased gamma-glutamyl transferase and in parallel alkaline phosphatase
Very rare: Haemoglobin decreased, platelet increased, white blood cell count decreased, gamma-glutamyl transferase increased, transaminase increased.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

4.9 Overdose

No specific effects of acute overdose are known (apart from rhabdomyolysis). There is no specific antidote. Thus appropriate symptomatic therapy is recommended in cases of overdose. In cases of rhabdomyolysis, bezafibrate must be stopped immediately and renal function carefully monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C10AB02

Mechanism of Action:
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 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.

Clinical efficacy and safety:
No data available.

5.2 Pharmacokinetic properties

Absorption

Bezafibrate is rapidly and almost completely absorbed from the standard tablet formulation. A peak plasma concentration of about 14mg/L is reached after 2 hours following ingestion of 2 x 200 mg standard tablets given as a single dose in healthy volunteers. With bezafibrate 400 mg modified release tablets, a peak concentration of about 8 mg is reached after about 4 hours. The relative bioavailability of bezafibrate retard compared to the standard form is about 70%.

Distribution

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

Biotransformation

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

Elimination

Elimination is rapid with excretion almost exclusively renal. 95% of the activity of ^{14}C-labelled drug is recovered in the urine and 3% in the faeces within 48 hours. 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/h.
The apparent half-life of bezafibrate prolonged-release tablets is about 2-4 hours.

Pharmacokinetics in Special Populations
The elimination of bezafibrate is reduced in patients with impaired renal function and dosage adjustments may be necessary to prevent drug accumulation and toxic effects (see section 4.2).
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).
In older people, there is a physiogical reduction of the renal function with age. Bezafibrate dosage should be adjusted based on the serum creatinine and creatinine clearance values) see section 4.2).
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 dosage was in the order of 30 to 40 times the human dosage. No such effect was apparent at reduced intake levels approximating more closely to the lipid-lowering dosage in human.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core: Polyethylene oxide, magnesium stearate, silica colloidal anhydrous
Film Coat: talc, hypromellose, macrogol 4000, titanium dioxide (E171).

6.2 Incompatibilities

Not Applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

Blister packs comprised of PVC/PVDC/aluminium strips enclosed in an outer carton containing 28 or 30 tablets.

6.6. Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited,
Park View, Riverside Way,
Watchmoor Park, Camberley,
Surrey,
GU15 3YL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0325

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2003 / 18/02/2009

10 DATE OF REVISION OF THE TEXT

16/09/2021