SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Bezafibrate 400
sustained release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bezafibrate 400 sustained release tablets
1 film-coated tablet contains 400 mg bezafibrate

For the list of excipients, see paragraph 6.1.

3. PHARMACEUTICAL FORM

Bezafibrate 400 sustained release tablets
Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hyperlipidemia of types IIa, IIb, III, IV, V in patients where diet alone is insufficient.

4.2 Posology and method of administration

Bezafibrate 400 retard film-coated tablets:
1 film-coated tablet to be taken once daily (morning or evening).

Note:
Patients with renal insufficiency (serum creatinine values > 1.5 mg/dl or creatinine clearance < 60 ml/min) must not use Bezafibrate400 mg retard film-coated tablets.

The coated tablets must not be chewed and must be taken with sufficient water either at mealtimes or after meals.

Dosage table

Serum creatinine	**Creatinine clearance**	**Bezafibrate400 mg retard tablets**
up to 1.5 mg/dl up to 135 µmol/l	over 60 ml/min	1 film-coated tablet/day
1.6 - 2.5 mg/dl 136 - 225 µmol/l	60 - 40 ml/min	contraindicated
2.6 - 6 mg/dl 226 - 530 µmol/l	40 - 15 ml/min	contraindicated
over 6 mg/dl over 530 µmol/l	less than 15 ml/min	contraindicated

Elderly patients:
In order to establish the right dosage, creatinine clearance should be determined, particularly in elderly patients.

Adults:
In adults creatinine clearance is calculated using the following equation (Cockroft and Gault) by taking serum creatinine, body weight and age into account:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age [years]} \times \text{body weight [kg]}}{72 \times \text{serum creatinine [mg/dl]}}$$

To calculate creatinine clearance in women, the value obtained using the Cockroft and Gault formula is multiplied by a factor of 0.85.

In patients with manifest *hypalbuminaemia* (as in patients with nephrotic syndrome), the dose should be further reduced. To prevent overdosing and overdose-induced rhabdomyolysis, bezafibrate plasma level determination is recommended to establish the correct dosage. Due to its high active substance content, Bezafibrate 400 mg retard film-coated tablets are contraindicated in these patients.

Bezafibrate400 mg retard film-coated tablets are contraindicated in dialysis patients.

Patients with liver diseases:
Except for fatty liver, which is the most common concomitant symptom in patients with hypertriglyceridaemia, Bezafibrate 400 mg retard film-coated tablets are contraindicated in all cases of liver diseases.

Children:
Bezafibrate dosage has not been adequately investigated in children.

4.3 Contra-indications

- Liver diseases (except for fatty liver, which is the most common concomitant symptom in hypertriglyceridaemia);
- gallbladder diseases with or without cholelithiasis (since liver involvement cannot be ruled out);
- known hypersensitivity to any components of the drug;
- known photoallergic or phototoxic reactions while on fibrate treatment;
- patients on dialysis.

Bezafibrate400 retard film-coated tablets**:**
- reduced kidney function with serum creatinine values exceeding 1.5 mg/dl or creatinine clearance below 60 ml/min.

4.4 Special warnings and special precautions for use

Besides hypertension and nicotine abuse, raised lipid blood levels are considered one of the most significant risk factors for incipient and progressive arteriosclerosis and its sequellae (coronary heart disease, impaired cerebral and peripheral blood circulation).

Before starting treatment for hyperlipidaemia, patients should always be given dietary recommendations and have their risk factors identified and corrected. In many cases, disorders of fat metabolism can be improved by a change in diet, weight reduction, increased physical activity, and the adequate treatment of other concurrent metabolic disorders. Such measures, if instituted before drug therapy, should be kept up during treatment with Bezafibrate400 mg retard film-coated tablets.

When establishing the diagnosis, it should be taken into account that blood lipid levels depend on different factors such as the time of day, the hour and nature of the last meal, alcohol intake, and stress.

Since oestrogens can lead to increased lipid levels, Bezafibrate400 mg retard film-coated tablets should be prescribed on an individual basis and only after careful consideration to patients on oestrogen or oestrogen-containing contraceptives.

Kidneys:
In patients with hypalbuminaemia, e.g. nephrotic syndrome, and those with renal insufficiency, Bezafibrate400 mg retard film-coated tablets should be replaced with lower-dose bezafibrate and kidney function monitored on a regular basis. Patients with pre-existing kidney insufficiency may suffer acute kidney failure if they do not strictly follow the prescribed dosage regimens based on determinations of their serum creatinine levels or their creatinine clearance.
Since drug treatment for hyperlipidaemia signifies long-term treatment in most cases, careful individual consideration should be given before instituting such a treatment in these patients.

Muscles:
Myotoxic effects and very rarely cases of rhabdomyolysis have been reported with the use of fibrates and other lipid-lowering agents. The incidence of myotoxicity is increased in patients with hypalbuminaemia and renal insufficiency in their medical history. Diffuse myalgia, myositis, muscle spasms, muscular weakness and/or significant increases in creatine phosphokinase (CPK) (more than a ten-fold increase above the norm) point to myotoxicity, in which case treatment with the drug must be ceased.
The risk of myotoxicity is increased if the drug is combined with another fibrate or a HMG-CoA reductase inhibitor (statin). This applies particularly if myopathy is already present. For this reason, the combination of bezafibrate with a statin should be limited to patients with severe combined hyperlipidaemia and increased cardiovascular risk who have not yet suffered from myopathy. This combination treatment should be instituted with care, and patients should be closely monitored for myotoxicity (see 4.5 Interaction with other medicinal products and other forms of interactions).

Liver:
As with other lipid-lowering drugs, elevated transaminase levels have been reported in some patients treated with bezafibrate. In the majority of cases observed the elevations were transient, slight and asymptomatic. It is recommended that patients' transaminase levels be checked every 3 months during the first year of treatment.
Patients who have been diagnosed with raised transaminase blood levels should be carefully monitored. Treatment should be ceased if SGOT and SGPT levels increase by more than three-fold the upper limit of the norm.

Pancreas:
Cases of pancreatitis have been reported during treatment with bezafibrate. In patients with severe hypertriglyceridaemia, this may be due to the lack of efficacy, direct side effect or cholelithiasis-mediated secondary effect of the drug with obstruction of the common bile duct.

Children:
Children should only be treated with bezafibrate following accurate diagnosis, since little is known regarding long-term tolerability in children.

Prescription of the drug during lactation is not recommended (see paragraph 4.6 Pregnancy and lactation).

Patients with a rare hereditary intolerance to galactose, lactase deficiency or glucose-galactose malabsorption must not take Bezafibrate400 mg retard film-coated tablets.

4.5 Interaction with other medicinal products and other forms of interaction

As with other fibrates, bezafibrate must not be combined with HMG-CoA reductase inhibitors due to the risk of rhabdomyolysis.

The product should not be administered together with perhexiline hydrogenmaleate or MAO- inhibitors.

Patients taking cholestyramine and Bezafibrate400 mg retard film-coated tablets concurrently should wait for at least 2 hours between taking both drugs, since cholestyramine affects the absorption of bezafibrate.

A significant but reversible reduction of kidney function (with a corresponding increase in serum creatinine) following the concurrent use of fibrate-containing drugs has been reported in some patients who had undergone an organ transplant and had been on immunosuppressant treatment. For this reason, kidney function should be carefully monitored in these patients and treatment with Bezafibrate400 mg retard film-coated tablets should be ceased where appropriate in case of significant changes in laboratory findings.

Bezafibrate can potentiate the action of coumarin-type anticoagulants. For this reason, the anticoagulant dose should be reduced by 30 - 50% at the beginning of treatment with bezafibrate and re-adjusted once blood coagulation is under control. Re-adjustment of the anticoagulant dose is also required following cessation of bezafibrate treatment.

Bezafibrate can potentiate the action of oral blood sugar-lowering drugs (e.g. sulphonyl ureas) and insulin.

Bezafibrate influences the effects of phenytoin.

4.6 Pregnancy and lactation

Pregnancy:
No data are available on Bezafibrate 400 mg retard film-coated tablets in exposed pregnant women. For this reason, the drug should only be prescribed during pregnancy following a careful benefit/risk assessment, for example to female patients exposed to the risk of acute pancreatitis because of severe hypertriglyceridaemia (> 10 g/l).

Animal experiment studies have given no indications of any teratogenic effect for Bezafibrate400 mg retard film-coated tablets.

Lactation:
No information is available on the excretion of Bezafibrate 400 mg retard film-coated tablets in maternal milk. In principle, it is not recommended that the drug be prescribed during lactation (see 4.4 Special warnings and special precautions for use).

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following undesirable effects may occur during treatment with Bezafibrate400 mg retard film-coated tablets:

Skin and skin appendages
Occasionally, allergic skin reactions such as pruritus, urticaria and other skin manifestations may occur. In isolated cases, generally reversible photoallergic or phototoxic reactions may occur, even after several months of complication-free treatment, in association with erythema, pruritus, blister formation and lichenoid changes. Very rarely, erythema multiforme, Stevens- Johnson syndrome and toxic epidermal necrolysis may occur. In this case, treatment with Bezafibrate400 mg retard film-coated tablets must be stopped immediately and appropriate treatment measures instituted.

Gastrointestinal tract
Occasionally, gastrointestinal disorders, such as sensation of fullness, nausea and loss of appetite, can occur.

Nervous system
Occasionally, headaches and dizziness may occur.
The above side effects are generally transient and do not require cessation of treatment.

Liver
In isolated cases, impaired liver function (e.g. increase in transaminases, cholestasis) has been observed.

Blood
In isolated cases a slight drop in haemoglobin and leukocyte count has been observed. A drop in platelet count with haemorrhage in some cases (e.g. purpura) has also been observed in isolated cases. Isolated cases have also been reported of a simultaneous drop in all three blood-cell elements (pancytopenia).

Miscellaneous
In rare cases, hair loss, and in isolated cases, impaired potency have occurred.

Most of the above-mentioned side effects generally rapidly subsided following cessation of treatment with Bezafibrate400 mg retard film-coated tablets.

Hypersensitivity
In isolated cases, generalised hypersensitivity reactions associated with tightness in the chest, dyspnoea, tachycardia, skin manifestations, hypotension, oedema, cardiovascular collapse, shivering and syncope have been observed. These allergic reactions require appropriate emergency treatment measures as well as the immediate cessation of treatment.

Kidneys
Long-term treatment frequently leads to slight elevations of serum creatinine.

Muscles
An important but rare side effect is myotoxicity associated with muscular pains, muscle weakness and muscle spasms. Creatine phosphokinase (CPK) must be determined in such cases. Rarely, significant CPK elevations can occur along with clinical symptoms of drug-related rhabdomyolysis. This is often due to excessively high doses, due for example to accumulation of the drug in patients with renal insufficiency (see paragraph 4.2. Posology and method of administration). In case of suspected rhabdomyolysis, treatment with bezafibrate should be suspended immediately and kidney function monitored carefully.

Gallbladder
Bezafibrate alters the composition of bile. Whether, as has been observed with other drugs with similar action, long-term treatment with bezafibrate leads to an increase in gallstones, or whether the gallstones present during treatment with bezafibrate increase in size, is disputed. Gallstone formation has been reported in isolated cases.

Abnormal laboratory findings
The following abnormal laboratory findings have been reported during clinical studies and in the post-marketing phase:
Elevation of transaminase levels (occasionally).

4.9 Overdose

There are no known symptoms of poisoning. Where appropriate, symptomatic treatment should be instituted.
There is no known specific antidote.

In case of suspected overdosing and rhabdomyolysis, treatment must be stopped. In patients with healthy kidneys, accelerated elimination may be attempted through forced diuresis. In case of rhabdomyolysis, patients should be given adequate liquids to prevent the development of a crush syndrome.

It is not possible to dialyse bezafibrate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmakotherapeutic group: lipid-lowering agent, ATC Code: C10A B02

Bezafibrate lowers elevated blood fat levels (triglycerides and cholesterol). It lowers elevated VLDL and LDL concentrations and increases HDL levels. The activity of the triglyceride lipases involved in the breakdown of triglyceride-rich lipoproteins (lipoprotein lipase and hepatic lipoprotein lipase) is increased by the action of bezafibrate. HDL precursors develop during the accelerated breakdown of triglyceride-rich lipoproteins (chylomicrons, VLDL), which explains the increase in HDL levels. Bezafibrate also reduces cholesterol biosynthesis, in parallel to which, it stimulates the LDL receptor-mediated lipoprotein breakdown.

Bezafibrate also acts on thrombogenic factors: besides a decrease in platelet aggregation, it also achieves a significant lowering of elevated fibrinogen levels and blood viscosity.

The consensus conference of the European Atherosclerosis Society in Naples in June 1986 undertook to establish limits for disorders of fat metabolism that are to be used as guidelines for diagnosis and treatment:

In all adults, cholesterol and triglyceride levels warrant medical attention if they exceed 200 mg/dl.

The overall risk for coronary heart disease, taking into account family history, smoking habits, hypertension, diabetes mellitus, male sex, younger age and lower HDL cholesterol levels below 35 mg/dl, is estimated to be with cholesterol levels of between 200 and 300 mg/dl. (HDL = higher density lipoproteins, half of which consist of protein [apolipoprotein]. They play a role in the breakdown of triglyceride-rich lipoproteins [chylomicrons and VLDL] and in the removal of cholesterol from the arteries' endothelial cells.)

The following is recommended in patients with HDL cholesterol levels below 35 mg/dl and/or with other risk factors present:

For most people with cholesterol levels between 200 and 250 mg/dl, dietary advice and the treatment of the other risk factors present are recommended. For people with severe hypercholesterolaemia (250 - 300 mg/dl) intensive dietary treatment and, where necessary, drug therapy with regular monitoring of effects are recommended.

In isolated cases exhibiting increased triglyceride levels (200 - 500 mg/dl) the cause of the hypertriglyceridaemia should be investigated.

Cases of extreme hyperlipidaemia (cholesterol exceeding 300 mg/dl, triglycerides exceeding 500 mg/dl) require a secondary diagnosis from specialists in fat metabolism.

Drug therapy is only indicated if hyperlipoproteinaemia cannot be rectified despite adopting consistent non-drug measures, or by treating an existing primary disease such as diabetes mellitus, gout or other disease.

In diabetics, decreased glucose blood levels as a result of improved glucose tolerance have been reported. In these patients, both fasting and postprandial free fatty acid concentrations were reduced.

5.2 Pharmacokinetic properties

Absorption and distribution
Following the administration of the non-sustained-release formulation of bezafibrate, absorption of the active substance is rapid and almost complete. Following a single dose of 200 mg in healthy subjects, peak plasma levels are approx. 8 mg/l after 1 - 2 hours.

Following the administration of 400 mg bezafibrate in sustained-release formulation, peak plasma concentrations are approx. 6 mg/l after 3 - 4 hours.

In human serum, bezafibrate is 94 - 96% protein-bound. The apparent distribution volume is approx. 17 l.

Metabolism and elimination
Bezafibrate is rapidly and almost entirely eliminated via the kidneys, some of it in metabolised form. A study in volunteers showed that following oral administration, 95% of active ^{14}C-labelled bezafibrate is excreted in the urine and 3% in the faeces within 48 hours. 50% of the administered dose appears in urine as unchanged bezafibrate, 20% in the form of glucuronides. Renal clearance is 3.4 to 6.0 l/hr. The average elimination half-life is 1 to 2 hours. The half-life of bezafibrate using the sustained-release formulation is approx. 2 to 4 hours.

The elimination of bezafibrate is slowed down in patients with renal insufficiency. To prevent the accumulation of bezafibrate and its toxic effects, the dosage should be adjusted in patients with impaired kidney function (see paragraph 4.2. Posology and method of administration). The elimination half-life of bezafibrate is prolonged in patients with reduced creatinine clearance.

Pharmacokinetic studies show that the elimination of bezafibrate can be slowed down in elderly subjects with impaired liver function. The use of bezafibrate is contraindicated in patients with liver diseases (except for fatty liver).

Dialysis
Bezafibrate cannot be dialysed (cuprophan filter).

Bioavailability
Following oral administration, bezafibrate is almost entirely absorbed. The relative bioavailability of the sustained-release compared to the non-sustained-release formulation is approx. 70%.

5.3 Pre-clinical safety data

Chronic toxicity tests have given no relevant indications of any specific toxicity for bezafibrate.

Bezafibrate mutagenicity tests turned out negative.

Rats and mice on high doses were found to have liver tumours caused by peroxisome proliferation. These changes are specific to small rodents and were not observed in other animal species. They have no relevance for the therapeutic use of bezafibrate in man. Tests in rats and rabbits have given no indications of any teratogenic effects. Embryotoxic effects have been observed at doses lying within the maternal toxic range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bezafibrate 400 mg retard film-coated tablets:
Lactose monohydrate, maize starch, macrogol 6000, talc, titanium dioxide E 171, magnesium stearate, polysorbate 80, hypromellose, sodium starch glycollate type A, polyacrylate dispersion 30%

6.2 Incompatibilities

None known

6.3 Shelf life

The shelf life of Bezafibrate400 mg retard film-coated tablets is 5 years. This

medicinal product must not be used after the expiry date.

6.4 Special precautions for storage

Below 25 º C

6.5 Nature and contents of container

Bezafibrate400 mg retard film-coated tablets:
30 film-coated tablets

6.6 Instructions for use/handling

None.

7. MANUFACTURER

Hennig Arzneimittel GmbH & Co. KG
Liebigstr. 1-2
65439 Flörsheim

8.LICENSE HOLDER and IMPORTER

Medison Pharma Ltd. POB 7090 Petach Tikva

9. DATE OF REVISION OF THE TEXT

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