

1. Name of the medicinal product

NORLIP

Bezafibrate 200mg Tablets

2. Qualitative and quantitative composition

Bezafibrate 200mg

3. Pharmaceutical form

Tablet for oral use.

Norlip is a white film-coated biconvex circular tablet with breakline on one side.

4. Clinical particulars

4.1 Therapeutic indications

Reduction of elevated blood levels of cholesterol and triglycerides.

4.2 Posology and method of administration

Adults

The recommended dosage for Norlip tablets is one tablet three times a day, equivalent to 600 mg bezafibrate. Each tablet ~~should be swallowed whole~~ with sufficient fluid after a meal. Occasionally gastro-intestinal symptoms may occur. In susceptible patients a slowly increasing dosage over 5 to 7 days may help to avoid such symptoms.

Elderly

In elderly patients there is a physiological reduction of the renal function with age. Bezafibrate dosage should be adjusted based on serum creatinine clearance values (see *Renal impairment* below).

Children

At present there is inadequate information regarding an appropriate dosage in children.

Renal impairment

In dialysis patients the use of bezafibrates is contraindicated.

In patients with renal insufficiency the dose should be adjusted according to serum creatinine levels or creatinine clearance as shown in the following table;

Serum creatinine ($\mu\text{mol/l}$)	Creatinine clearance (ml/min)	Dosage (tablets/day)
Up to 135	Over 60	3
136 – 225	60 – 40	2
226 – 530	40 – 15	1 every 1 or 2 days
Over 530	Less than 15	Contraindicated

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 Treatment should be withdrawn if an adequate response has not been achieved within 3 to 4 months.

4.3 Contraindications

- Significant hepatic disease (other than fatty infiltration of the liver associated with raised triglyceride values).
- Gall-bladder diseases with or without cholelithiasis.
- Patients with nephrotic syndrome and severe renal failure (serum creatinine $> 530\mu\text{mol/l}$; creatinine clearance $< 15\text{ml/min}$) and patients undergoing dialysis (see section 4.2).
- Combination therapy of bezafibrate with HMG CoA reductase inhibitors in patients with predisposing factors for myopathy (see sections 4.4. and 4.5)
- Known hypersensitivity to bezafibrate, to 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, nephritic 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, elderly (aged >65 years), personal or 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 *Undesirable effects*).
- 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 Norlip 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 Norlip.

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 Norlip 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 Pregnancy and lactation

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

There is insufficient information on the excretion of bezafibrate or its metabolites in human 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 Norlip 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

Norlip 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 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 in the table below. Frequency of reporting: Common ($\geq 1/100$ and $<1/10$), Uncommon ($\geq 1/1,000$ and $<1/100$), Rare ($\geq 1/10,000$ and $<1/1000$), 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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No specific effects of acute overdose are known. Rhabdomyolysis has occurred. 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 hyperfibrinogenemic 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.

Efficacy / Clinical Studies:

No data available.

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 8mg/L is reached after 1–2 hours following a single 200mg dose in healthy volunteers.

Distribution

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

Metabolism

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. Ninety-five percent of the activity of the ¹⁴C-labelled drug is recovered in the urine and 3% in the faeces within 48 hours. 50% 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 6.0L/h.

The elimination half-life of bezafibrate is 1-2 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 (see 4.3 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 above table.

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

Not surprisingly 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.

5.3 Preclinical safety data

The chronic administration of a high dose of bezafibrate to rats was associated with hepatic tumour formation in females. This 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 humans.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose; Maize starch; Pregelatinized starch; Colloidal silicone dioxide; Sodium starch glycollate; Magnesium stearate; Opadry.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 month.

6.4 Special precautions for storage

Store below 25 °C and protect from light.

6.5 Nature and contents of container

The container is a blister, which is made of a polyvinylchloride base film and an aluminium cover foil. Pack sizes: 10,15,20,30 tablets, not all the pack sizes are marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Unipharm Ltd., P.o.b 21429, Tel-Aviv, 6121301.

8. Marketing authorisation number(s)

046 05 23778 01

9. Date of first authorisation/renewal of the authorisation

02/2016

10. Date of revision of the text

01/03/2016