NORLIP

1 NAME OF THE MEDICINAL PRODUCT

Norlip Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Norlip tablet contains 200mg of bezafibrate

Excipient with known effect:

Norlip contains 10mg Sodium starch glycolate (also see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Norlip 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 Norlip 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.

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.

Serum creatinine	*Creatinine clearance*	*Dosage (Norlip 200 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)
1.6 – 2.5 mg/100 ml (136 – 225 micromol/l)	60 – 40 ml/min	2 film coated tablets/day (1 tablet twice daily)
2.6 – 6 mg/100 ml (226 – 530 micromol/l)	40 – 15 ml/min	1 film coated tablet every 1 or 2 days
Over 6 mg/100 ml (Over 530 micromol/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:

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

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 Norlip is contraindicated. Norlip 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. Norlip dosage should be adjusted according to the serum creatinine and creatinine clearance values as indicated in the above table.

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 Norlip is normally a long term therapy.

Method of administration
Norlip tablets should be swallowed with sufficient fluid, with or after meals.

4.3 Contraindications

- Hypersensitivity to the active substance, other fibrates, or to any of the excipients listed in section 6.1.
- 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 > 530μmol/l; creatinine clearance <15ml/min) and patients undergoing dialysis (see section 4.2).
- Combination therapy of Norlip with HMG CoA reductase inhibitors in patients with predisposing factors for myopathy (see sections 4.4. and 4.5)
- Known photoallergic or phototoxic reactions to fibrates.

4.4 Special warnings and precautions for use

- Norlip 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 Norlip therapy is initiated.
- Norlip 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 Norlip 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 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).
- Norlip 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).

- Norlip alters the composition of bile. There have been isolated reports of the development of gallstones.
- As Norlip 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 Norlip in patients taking oestrogens or oestrogen-containing contraceptives must be critically considered on an individual basis.
- When Norlip is given in combination with anion-exchange resins (e.g. colestyramine), the two drugs should be taken at least 2 hours apart.

Excipient(s)

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 Norlip 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 Norlip 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 Norlip. Accordingly, renal function should be closely monitored in these patients and, in the event of relevant significant changes in laboratory parameters, Norlip, should if necessary, be discontinued.

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

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

Fertility and pregnancy

There are limited data from the use of Norlip 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.

Breast-feeding

There is insufficient information on the excretion of Norlip 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 Norlip is based on a combination of clinical study data and post-marketing experience.

The frequency of adverse drug reactions (ADRs) 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).

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
http://forms.gov.il/globaldata/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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, Norlip 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.

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 liters.

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. Ninety-five percent of the activity of the ^{14}C-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. 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 humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Maize starch, Pregelatinized starch, Sodium starch Glycolate, Magnesium stearate, Colloidal silicone dioxide, Opadry White Y-1-7000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packing materials.

6.4 Special precautions for storage

Store below 25ºC and in a place protected from light.

6.5 Nature and contents of container

Packs of 50, 60, 100 or 1,000 tablets in PVC/Aluminium blister strips.
Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Unipharm ltd, 1 Shevet Shimon St. P.O. Box 16545, Tel Aviv, 6116401, Israel.

Manufacturer: Unipharm Ltd., "Mevo Carmel" Industrial Park.

8 MARKETING AUTHORISATION NUMBER(S)

046-05-23778-02

9 DATE OF REVISION OF THE TEXT

Revised in September 2024.