SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LIPANOR 100 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg ciprofibrate as the active ingredient.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Capsules.
Each capsule contains an opaque olive green cap and an opaque cream body, containing white to off-white odourless powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of primary hyperlipidaemia resistant to appropriate dietary management, including hypercholesterolaemia, hypertriglyceridaemia and combined hyperlipidaemia.

4.2 Posology and method of administration

Adults*:* The recommended dosage is one capsule (100 mg ciprofibrate) per day. This dose should not be exceeded (See Precautions)

Elderly patients: As for adults, but see Precautions and Warnings.

Use in Case of impaired renal function*:* In moderate renal impairment (creatinine clearance 30-80 ml/min/1.73m2) it is recommended that dosage be reduced to one capsule every other day. Patients should be carefully monitored. Ciprofibrate should not be used in severe renal impairment (creatinine clearance <30 ml/min/1.73m2)

Use in Children: Not recommended since safety and efficacy in children have not been established.

For oral administration only

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance <30 ml/min/1.73m2)
- Pregnancy and lactation, or when pregnancy is suspected.
- Concurrent use with another fibrate.
- Previous phototoxicity caused by fibrates

4.4 Special warnings and special precautions for use

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Myalgia/myopathy:

- Patients should be advised to report unexplained muscle pain, tenderness or weakness immediately.

CPK levels should be assessed immediately in patients reporting these symptoms. Therapy should be discontinued if myopathy is diagnosed or if markedly elevated CPK levels (levels exceeding 5 times the normal range) occur.

- Doses of 200mg ciprofibrate per day or greater have been associated with a high risk of rhabdomyolysis. Therefore the daily dose should not exceed 100mg.

- The risk of myopathy may be increased in the presence of the following predisposing factors:

- impaired renal function and any situation of hypoalbuminaemia such as nephrotic syndrome
- hypothyroidism or untreated hypothyroidism
- alcohol abuse
- age > 70 years
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another fibrate

- As with other fibrates, the risk of rhabdomyolysis and myoglobinuria may be increased if ciprofibrate is used in combination with other fibrates or HMG CoA reductase inhibitors (see sections 4.3 and 4.5).

Use with caution in patients with impaired hepatic function.

Periodic hepatic function tests are recommended (every 3 months for the first 12 months of treatment). Ciprofibrate treatment should be discontinued in case of increased AST and ALT levels to more than 3 times the upper limit of normal or if cholestatic liver injury is evidenced.

Secondary causes of dyslipidaemia, such as hypothyroidism, should be excluded or corrected prior to commencing any lipid lowering drug treatment.

In patients with hypertriglyceridaemia, ciprofibrate may cause an increase of the LDL level.

Special precautions for use

Association with oral anticoagulant therapy: concomitant oral anticoagulant therapy should be given at reduced dosage and adjusted according to INR (see section 4.5).

If after a period of administration lasting several months, a satisfactory reduction in serum lipid concentrations has not been obtained, additional or different therapeutic measures must be considered.

4.5 Interactions with other medicinal products and other forms of interaction

Other fibrates: As with other fibrates, the risk of rhabdomyolysis and myoglobinuria may be increased if ciprofibrate is used in combination with other fibrates (see sections 4.3 and 4.4.).

• Not recommended combinations

HMG CoA reductase inhibitors: As with other fibrates, the risk of myopathy, rhabdomyolysis and myoglobinuria may be increased if ciprofibrate is used in combination with HMG CoA reductase inhibitors (see section 4.4). The benefits of combined use should

be carefully weighed against the risks. Physicians contemplating concomitant therapy with HMG-CoA reductase inhibitors should consult the SPC of the relevant HMG CoA reductase inhibitor as some higher doses are contraindicated/ not recommended with fibrates.

• **Combination requiring caution**
Oral anticoagulant therapy: Ciprofibrate is highly protein bound and therefore likely to displace other drugs from plasma protein binding sites. This may increase the effects of drugs like phenytoin, tolbutamide and other sulphonylurea derivatives and coumarin-like anticoagulants. Ciprofibrate has been shown to potentiate the effect of warfarin, indicating that concomitant oral anticoagulant therapy should be given at reduced dosage and adjusted according to INR (see section 4.4).

• **Combination to be taken into account**
Cholestyramine and colestipol may reduce the absorption of ciprofibrate. These drugs should not be taken together or close to each other.

No clinically relevant interactions exist with cytochrome P450, beta blocking agents, calcium antagonists, diuretics, other hypertensives digoxin and nitroglycerin

Oral hypoglycaemics: Although ciprofibrate may potentiate the effect of oral hypoglycaemics, available data do not suggest that such an interaction may be clinically significant.

Oesrogens: Oestrogens can raise lipid levels. Although pharmacodynamic interaction may be suggested, no clinical data are currently available.

4.6 Pregnancy and lactation

Pregnancy
There are insufficient data from the use of ciprofibrate in pregnant women.
Animal studies have demonstrated neonatal thrombosis (see section 5.3). The potential risk for humans is unknown. Ciprofibrate is contraindicated during pregnancy (see section 4.3)

Lactation
Ciprofibrate is contraindicated during breast-feeding (see section 4.3). It is not known if ciprofibrate is excreted into breast milk.

Fertility
There are no data on the effects of ciprofibrate on fertility in humans.

4.7 Effects on ability to drive and use machines

Dizziness, somnolence and fatigue have only rarely been reported in association with ciprofibrate. Patients should be warned that if they are affected they should not drive or operate machinery.

4.8 Undesirable effects

The adverse reactions observed in clinical studies and reported in post-marketing experience are detailed below. Post-marketing adverse reactions are designated with a frequency “not known”.
Adverse reactions frequency is defined using the following convention: Very common (≥

1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

	Rare	Very rare	Not known
Blood and lymphatic system disorders			Leukocytopenia Thrombocytopenia
Nervous system disorders	Dizziness Somnolence		Headache Vertigo
Respiratory thoracic and mediastinal disorders			Pneumonitis or Pulmonary fibrosis (Isolated cases)
Gastrointestinal disorders			Nausea[2] Vomiting[2] Diarrhoea[2] Dyspepsia[2] Abdominal pain[2]
Hepatobiliary disorders		Cholestasis or Cytolysis[3]	Cholelithiasis[3]
Skin and subcutaneous tissue disorders		Photosensitivity	Rash, urticarial, pruritis and eczema (mainly allergic) Alopecia
Musculoskeletal and connective tissue disorders	Rhabdomyolysis[1]		Myalgia[1] and myopathy[1]including myositis[1]
Reproductive system and breast disorders			Erectile dysfunction
General disorders and administration site conditions	Fatigue		
Investigations			Blood creatine phosphokinase increased Liver function test Abnormal[3]

[1]In the majority of cases muscle toxicity is reversible when treatment is withdrawn (see section 4.4).
[2]Generally, these side effects were mild to moderate in nature and occurred early on, becoming less frequent as treatment progressed.
[3]As with other fibrates, abnormal hepatic function tests have been observed occasionally. Very rare cases of cholestasis or cytolysis have been reported (see section 4.4). Exceptional cases with chronic evolution have been observed. Some cases of

cholelithiasis have been reported.

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 https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms
Overdosage with ciprofibrate has been rarely reported. Some cases of overdose are known, but in these cases, no adverse reactions specific to overdose have been observed. In the worst case, after ingestion of 2800 mg ciprofibrate for 3 days, rhabdomyolysis observed.

Treatment
There are no specific antidotes to ciprofibrate. Treatment of overdosage should be symptomatic. The usual measures should be taken to prevent further absorption of the drug from the gastro-intestinal tract. Gastric lavage and appropriate supportive care may be instituted if necessary. Ciprofibrate is nondialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C10A B08
Pharmacotherapeutic group: Serum lipid reducing agents - fibrates.

Ciprofibrate is a new derivative of phenoxyisobutyric acid which has a marked hypolipidaemic action. It reduces both LDL and VLDL and hence the levels of triglyceride and cholesterol associated with these lipoprotein fractions. It also increases levels of HDL cholesterol. The mechanism of action of ciprofibrate is not entirely clear. It includes increased VLDL catabolism, but may also be influenced by reduced synthesis of VLDL or direct effect on the LDL receptor

Ciprofibrate is effective in the treatment of hyperlipidaemia associated with high plasma concentrations of LDL and VLDL (types IIa, IIb, III and IV according to the Fredrickson Classification). In clinical studies ciprofibrate has been shown to be effective in complementing the dietary treatment of such conditions.

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 and Distribution

Ciprofibrate is readily absorbed in man, with maximum plasma concentrations occurring mainly between one and four hours following an oral dose. Following a single dose of 100mg, in volunteers, maximum plasma concentration of ciprofibrate was between 21 and 36µg/ml. In patients on chronic therapy, maximum levels from 53 to 165µg/ml have been measured. The plasma protein binding of ciprofibrate is about 98% in the therapeutic

range.

Elimination

Terminal elimination half-life in patients on long term therapy varies from 38 to 86 hours. The elimination half-life in subjects with moderate renal insufficiency was slightly increased compared with normal subjects (116.7h compared with 81.1h). In subjects with severe renal impairment, a significant increase was noted (171.9h).

Approximately 30-75% of a single dose administered to volunteers was excreted in the urine in 72 hours, either as unchanged ciprofibrate (20-25% of the total excreted) or as a conjugate. Subjects with moderate renal impairment excreted on average 7.0% of a single dose as unchanged ciprofibrate over 96 hours, compared with 6.9% in normal subjects. In subjects with severe insufficiency this was reduced to 4.7%.

5.3 Preclinical safety data

In animal studies with respect to reproduction neonatal thrombosis is seen in rats at doses similar to the therapeutic dosage. The potential risk for humans is unknown.
Other findings add nothing to the clinical experience.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Maize starch, gelatin, titanium dioxide, yellow iron oxide, black iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 25°C, cool and dry place

7. PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

10, 20, 30, 60 and 100 capsules.
Not all packages sizes may be marketed.
Registration number: 1055628758

8. MANUFACTURER

CTS Chemical Industries Ltd., 3 HAKIDMA ST. Kiryat-Malachi, Israel

9. DATE OF APPROVAL / REVISION

Revised in 05/2024 according to the MoH guidelines.