SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ciprofibrate 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg ciprofibrate as the active ingredient.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet.

White to off white round tablets with a breakline on one side and embossed 'S170' on the other

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofibrate 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

Adults

The recommended dosage is one tablet (100mg 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 it is recommended that dosage be reduced to one tablet every other day. Patients should be carefully monitored. Ciprofibrate should not be used in severe renal impairment.

Use in Children

Not recommended since safety and efficacy in children has not been established.

Ciprofibrate tablets are for oral administration only.

4.3 Contraindications

Severe hepatic impairment.

Severe renal impairment.

Pregnancy and lactation, or when pregnancy is suspected.

Concurrent use with another fibrate.

Hypersensitivity to the active substance or to any component of the product.

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose 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
- 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.

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 should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

- **Contra-indicated combination**

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. 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**

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

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

4.6 Pregnancy and lactation

Pregnancy

There is no evidence that ciprofibrate is teratogenic, but signs of toxicity at high doses were observed in teratogenicty tests in animals. As there are no data on its use in human pregnancy ciprofibrate is contraindicated during pregnancy.

Lactation

Ciprofibrate is excreted in the breast milk of lactating rats. As there are no data on its use in lactation, ciprofibrate is contraindicated in nursing mothers.

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).

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					Thrombocytopenia
Nervous system disorders	Headache Dizziness Somnolence Vertigo				
Respiratory thoracic and mediastinal disorders					Pneumonitis Pulmonary fibrosis
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Dyspepsia Abdominal pain				
Hepatobiliary disorders					Liver function test abnormal Cholestasis Cytolysis Cholelithiasis
Skin and subcutaneous tissue disorders	Rash Alopecia				Urticaria Pruritis Photosensitivity reaction Eczema
Musculoskeletal and connective tissue disorders	Myalgia				Elevation of serum creatine phosphokinase Myopathy Myositis Rhabdomyolysis
Reproductive system and breast disorders					Erectile dysfunction
General disorders and administration site conditions	Fatigue				

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continuous 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

There are rare reports of overdosage with ciprofibrate but in these cases there are no adverse events that are specific to overdosage. There are no specific antidotes to ciprofibrate. Treatment of overdosage should be symptomatic. Gastric lavage and appropriate supportive care may be instituted if necessary. Ciprofibrate is non-dialysable.

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.

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

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.

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

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, Lactose monohydrate, Microcrystalline cellulose, Hypromellose, Powdered vegetable stearine, Sodium laurilsulfate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years when packed in blister strips (see below).
48 months when packed in amber glass bottles.

6.4 Special precautions for storage

There are no special storage precautions.

6.5 Nature and contents of container

Clear PVC / Aluminium blister strips in packs of 28 tablets.

Amber glass bottles of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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PL 17780/0456

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 June 2009

10 DATE OF REVISION OF THE TEXT

30 January 2014