PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

FENOTIVO 200 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each FENOTIVO capsule contains 200 mg fenofibrate (micronised).

Excipients with known effect:

FENOTIVO contains sugar (40,95 mg sucrose per capsule).

FENOTIVO contains sodium (as sodium benzoate and sodium lauril sulfate) and propylene glycol.

Each capsule contains 0,003 % *m/m* sodium benzoate, as preservatives.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

FENOTIVO capsules are size 1 hard gelatin capsules having a yellow cap and clear transparent body filled with white to off-white spherical pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FENOTIVO is indicated for the reduction of triglycerides and cholesterol in the treatment of type IIa and IIb, type III and IV hyperlipoproteinaemias, when an appropriate diet has been followed but has not been sufficient, especially when the blood cholesterol remains elevated with dietary modifications, and/or when there are associated risk factors.

Before starting FENOTIVO treatment, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients or control of diabetes mellitus.

It has not been established whether the medicine-induced lowering of serum cholesterol or lipid levels have detrimental, beneficial or no effects on the morbidity or mortality due to atherosclerosis or coronary heart disease. Treatment with FENOTIVO should be discontinued if a significant lowering in serum lipids is not obtained.

4.2 Posology and method of administration

Individual adapted dietary measures should be instituted in combination with FENOTIVO treatment.

Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follow FENOTIVO treatment, but treatment should be discontinued if adequate response has not been achieved within three months.

Posology

The adult dosage is one capsule daily taken with one of the main meals.

Special populations

Elderly Patients

In elderly patients without renal impairment, the normal dose is recommended.

Paediatric population

The safety and efficacy of fenofibrate, as contained in FENOTIVO, in children and adolescents younger than 18 years has not been established. No data are available.

Therefore the use of fenofibrate, as contained in FENOTIVO, is not recommended in paediatric subjects under 18 years.

Method of administration

FENOTIVO should be swallowed whole during a meal.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Impaired renal function and renal lithiasis.
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality) and known gallbladder disease.
- Chronic or acute pancreatitis (with the exception of acute pancreatitis due to severe hypertriglyceridemia).
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- Pregancy and lactation.

4.4 Special warnings and precautions for use

Renal function

In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance. Use of a non-micronised fibrate is preferred in elderly patients with renal impairment where dosage reduction may be required.

Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or when used concurrently with statins (HMG CoA reductase inhibitors). It is reported that elevations in serum creatinine were generally stable over time with no evidence of continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment.

Treatment should be interrupted when creatinine level is 50 % above the upper limit of normal.

It is recommended that creatinine is monitored during the first 3 months after treatment initiation and periodically thereafter.

Liver function

FENOTIVO is contraindicated in hepatic insufficiency, including biliary cirrhosis and unexplained persistent liver function abnormality (see section 4.3).

Hepatitis has been reported infrequently. Increases in transaminase levels have been reported in some patients. In the majority of cases these elevations were transient, minor, asymptomatic and only interfered with treatment infrequently. However, it is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and periodically thereafter.

Attention should be paid to patients who develop an increase in transaminase levels and treatment should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, treatment should be discontinued.

Pancreas

Pancreatitis has been reported in patients taking fenofibrate, as contained in FENOTIVO (see sections 4.3 and 4.8). This may be due to efficacy failure in patients with severe hypertriglyceridaemia (i.e., a direct medicine effect) or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Muscle toxicity

Muscle toxicity, including cases of rhabdomyolysis, with or without renal failure, has been reported with the use of fibrates, as contained in FENOTIVO, and other lipid-lowering medicines.

The incidence of muscle toxicity increases in cases of hypoalbuminaemia and previous renal insufficiency. Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of

developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy, like FENOTIVO, should be carefully weighed up. Patients who are at risk or who show signs of muscle toxicity should be monitored closely and creatine phosphokinase (CPK) levels checked.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with FENOTIVO should be stopped.

The risk of muscle toxicity may be increased if FENOTIVO is used concurrently with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease (see section 4.5). Consequently, the co-prescription of FENOTIVO with an HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and a close monitoring of potential muscle toxicity.

Gallstones

Gallstones have occasionally been reported during treatment with fenofibrate, as contained in FENOTIVO, but any causal relationship remains inconclusive.

Monitoring

Monitoring of biological parameters should be regularly performed, especially renal function and liver function tests. Glucose tolerance should also be monitored.

Secondary causes of hyperlipidaemia

Secondary causes of hyperlipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before treatment with fenofibrate, as contained in FENOTIVO, is considered. Secondary cause of

hypercholesterolemia related to pharmacological treatment can be seen with diuretics, beta blockers, estrogens, progestogens, combined oral contraceptives, immunosuppressive medicines and protease inhibitors. In these cases it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by these therapeutic medicines).

Excipients

FENOTIVO contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take FENOTIVO.

FENOTIVO contains propylene glycol to a maximum of 0,0375 mg in each FENOTIVO capsule.

FENOTIVO contains 0,003 % *m/m* sodium benzoate, as preservative.

FENOTIVO contains less than 1 mmol sodium (23 mg) per capsule; that is to say it is essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

HMG-CoA reductase inhibitors or Other Fibrates

The risk of serious muscle toxicity is increased if a fibrate, like FENOTIVO, is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity (see section 4.4).

There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin.

Oral anti-coagulants

Fenofibrate, as contained in FENOTIVO, enhances the effects of oral anti-coagulants and may increase the risk of bleeding. In patients receiving oral anti-coagulant therapy, the dose of anti-coagulant should be reduced by about one-third at treatment initiation and then gradually adjusted, if necessary, according to INR (International Normalised Ratio) monitoring.

Ciclosporin

Severe cases of reversible renal function impairment have been reported during concurrent use of fenofibrate, as contained in FENOTIVO, and ciclosporin. With concomitant use, renal function must therefore be closely monitored and treatment with FENOTIVO discontinued in the case of severe alteration of laboratory parameters.

Glitazones

Cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concurrent use of fenofibrate, as contained in FENOTIVO, and glitazones. Therefore, it is recommended to monitor HDL-cholesterol if one of these medicines is added to the other and discontinuing either therapy if HDL-cholesterol is too low.

Cytochrome P450 enzymes

In vitro studies using human liver microsomes report that fenofibrate, as contained in FENOTIVO, and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3M, CYP2D6, CYP2E1, or CYP1A2; are weak inhibitors of CYP2C19 and CYP2A6; and mild-to-moderate inhibtors of CYP2C9 at therapeutic concentrations.

Patients concurrently taking FENOTIVO with CYP2C19, CYP2A6 and / or CYP2C9 (especially) metabolised medicines with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of such medicines must be made.

Other

Fenofibrate, as contained in FENOTIVO, induces microsomal mixed-function oxidases involved in fatty acid metabolism in rodents and may interact with medicines metabolised by these enzymes.

Possible interactions with oral hypoglycaemic medicines should also be considered.

In vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites when used with fenofibrate, as contained in FENOTIVO.

4.6 Fertility, pregnancy and lactation

Pregnancy

FENOTIVO should not be used during pregnancy (see section 4.3).

Breastfeeding

It is unknown whether fenofibrate and/or its metabolites are excreted in human milk and risk to breastfeeding infants cannot be excluded. Therefore, FENOTIVO should not be used during breastfeeding (see section 4.3).

Fertility

Reversible effects on fertility have been observed in animals. However, there are no clinical data available on the effects of fenofibrate, as contained in FENOTIVO, on fertility.

4.7 Effects on ability to drive and use machines

The effect of fenofibrate, as contained in FENOTIVO, on the ability to drive and use machines is determined by adverse effects such as headache, fatigue and vertigo (see section 4.8). Patients should establish the effect of adverse effects before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are gastrointestinal disturbances, skin reactions, headache, fatigue and vertigo.

Listing of adverse reactions

Blood and lymphatic system disorders:

Less frequent:	Haemoglobin decreased, white blood cell count decreased.

Immune system disorders:

Less frequent:	Hypersensitivity.

Nervous system disorders:

Frequent:	Headache.

Ear and labyrinth disorders:

Frequent:	Vertigo.

Vascular disorders:

Less frequent:	Thromboembolism (pulmonary embolism, deep vein thrombosis).

Respiratory, thoracic and mediastinal disorders:

Frequency unknown:*	Interstitial lung disease.

Gastrointestinal disorders:

Frequent:	Gastrointestinal disturbances (abdominal pain, nausea, vomiting, diarrhoea, flatulence).

Less frequent:	Pancreatitis.

Hepatobiliary disorders:

Frequent:	Transaminases increased (see section 4.4).
Less frequent:	Cholelithiasis (see section 4.4), hepatitis.
Frequency unknown:*	Jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic).

Skin and subcutaneous tissue disorders:

Less frequent:	Cutaneous hypersensitivity (e.g., rash, pruritus, urticaria), alopecia, photosensitivity reactions.
Frequency unknown:*	Severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).

Musculoskeletal, connective tissue and bone disorders:

Less frequent:	Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness).
Frequency unknown:*	Rhabdomyolysis.

Reproductive system and breast disorders:

Less frequent:	Sexual dysfunction, sexual asthenia.

General disorders and administration site conditions:

Frequent:	Fatigue.

Investigations:

Frequent:	Blood homocysteine level increased.
Less frequent:	Blood creatinine increased, blood urea increased.

* For side effects that have been reported spontaneously during post-marketing use of fenofibrate, as contained FENOTIVO, a precise frequency cannot be estimated from the available data and is therefore classified as "frequency unknown".

Description of selected adverse reactions

Type 2 diabetic patients: pancreatitis and thromboembolism incidence

Results from a randomised placebo-controlled trial in patients with type 2 diabetes mellitus reported a significant increase in pancreatitis cases observed in patients receiving fenofibrate, as contained in FENOTIVO, as well as in the incidence of pulmonary embolism. An increase in the incidence of deep vein thromboses was also reportred; however, it was classified as a statistically non-significant increase.

Blood homocysteine level increase

Results from a randomised placebo-controlled trial in patients with type 2 diabetes mellitus reported an increase in blood homocysteine levels in patients treated with fenofibrate, as contained in FENOTIVO, with an average increase of 6,5 µmol/L which was reversible upon treatment discontinuation. The increased risk of venous thrombotic events may be related to the increased homocysteine level. However, the clinical significance of this is unclear.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting planform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

In the majority of reported cases no overdose symptoms have been reported.

Treatment of suspected overdose is symptomatic and supportive. No specific antidote is known. Fenofibrate, as contained in FENOTIVO, cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 7.5 - Serum cholesterol reducers.

Pharmacotherapeutic group: serum lipid reducing medicine/cholesterol and triglyceride reducers/fibrates.

ATC code: C10 AB 05.

Fenofibrate reduces elevated cholesterol as well as elevated triglyceride levels in type IIa and IIb, type IV and diet-resistant type III hyperlipidaemia. The reduction of cholesterol and triglyceride levels varies according to initial levels. The greatest reduction occurs in patients with major forms of hyperlipidaemia. The onset of the hypotriglyceridaemic effect precedes the hypocholesterolaemic effect and the maximum hypocholesterolaemic effect is obtained only after treatment of a period of at least three months.

Mechanism of action

Fenofibrate is a fibric acid derivative. Its lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type α (PPARα). Through activation of PPARα, fenofibrate increases lipolysis and elimination of atherogenic triglyceride rich particles from plasma by activating lipoprotein lipase and reducing production of Apoprotein C-111. Activation of PPARα also induces an increase in the synthesis of Apoproteins A-I and A-II.

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations (C_{max}) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual.

The absorption of fenofibrate is increased when administered with food.

Distribution

Fenofibric acid is strongly bound to plasma albumin (more than 99 %).

Biotransformation and excretion

After oral administration, fenofibrate is rapidly hydrolised by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma.

Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

It is excreted mainly in the urine and practically all is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronoconjugate.

In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.

It has been demonstrated that it does not accumulate, and the plasma elimination half-life of fenofibric acid is approximately 20 hours.

Fenofibric acid is not eliminated during haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules:

Cetyl Stearyl alcohol & ethoxylate

Dimethicone (polydimethylsiloxane)

Gelatin capsules (hard, size 1)

Hypromellose

Maize starch

Polysorbate (polyethylene glycol sorbitan monolaurate)

Povidone K-30

Propylene glycol

Purified Water

Simethicone

Sodium benzoate

Sodium lauril sulfate

Sugar

Talc

Capsule shells:

Gelatin

Iron Oxide Yellow (E171)

Purified water

Sodium lauril sulfate

Titanium dioxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in original packaging.

6.5 Nature and contents of container

FENOTIVO is packed in clear transparent PVC-Aluminium blisters, in pack sizes of 30 capsules, packed in outer unit cartons.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

57/7.5/0757

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 July 2025