LIPANTHYL® PENTA 145

145 mg Fenofibrate

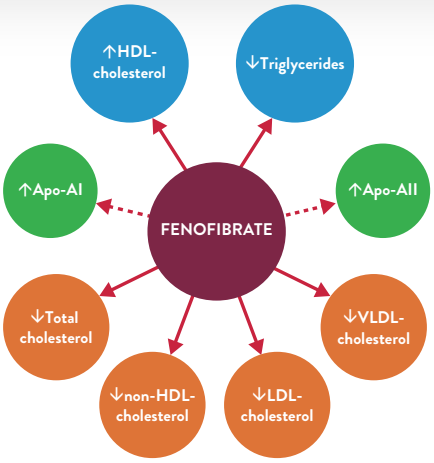
A STATIN LIPANTHYL FENOFIBRATE

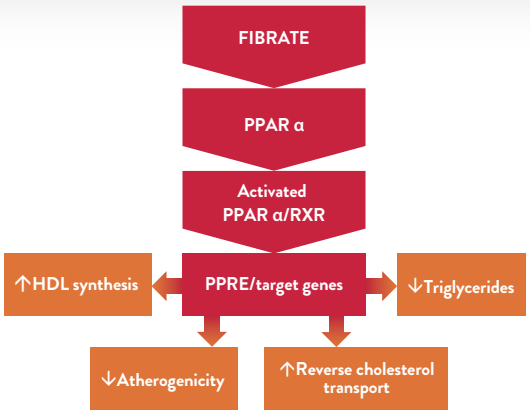
聯控風險 合力而安

Patient who achieve their LDL-C target with marginal TG (2.3-5.6 mmol/L), initiate co-statin treatment with Lipanthyl to achieve non-HDL-C target level and reduce CV risk

Abbott

Fenofibrate : For reduction of both CV risk and complications associated with elevated lipid profiles[1]





Fenofibrate mechanism of action

The effects of fenofibrate are mediated by its activation of the nuclear transcription factor PPARα.[1] Activated PPARα dimerises with another nuclear receptor, retinoid X receptor, which then complexes with peroxisome proliferator response elements (PPREs), modulating the expression of genes that regulate lipid metabolism (Figure 5)[1]

Activation of PPARα affects lipid metabolism in multiple ways.10 It increases lipolysis and elimination of TG-rich particles from the plasma via activation of lipoprotein lipase (LPL) and reduced production of Apo-CIII, an inhibitor of LPL. It also promotes the β-oxidation of fatty acids, which reduces the fatty acids available for TG synthesis. By reducing acetyl- CoA carboxylase and fatty acid synthase activity, fenofibrate inhibits de novo fatty acid synthesis and the production of TG.[1]

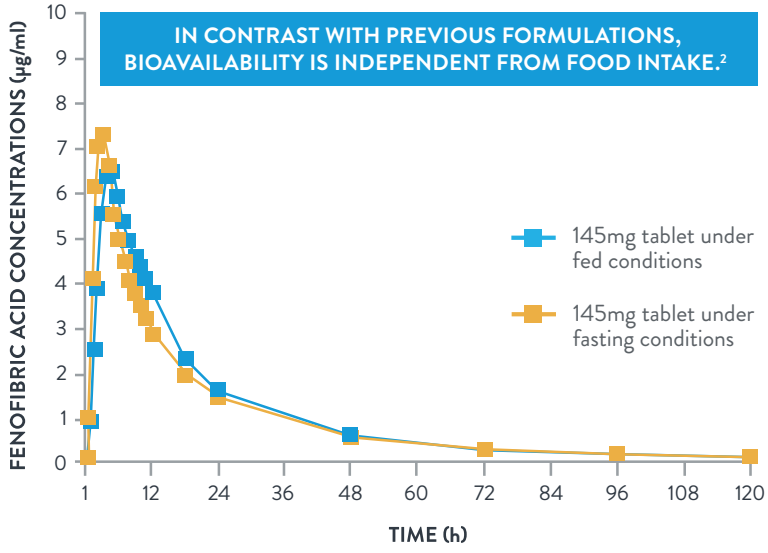
Fenofibrate reduces Apo-B and VLDL production and secretion, while increasing LDL clearance.[1]

Activation of PPAR α also promotes synthesis of the HDLassociated lipoproteins Apo-AI and Apo-AII, resulting in increased levels of HDL-C.[1]

Reference:
1. Keating GM, Croom KF. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. Drugs 2007; 67(1): 121–53.

LIPANTHYL® 145MG film-coated tablets contain fenofibrate nanoparticles[1] developed with nanocrystal® technology[2]

NO FOOD EFFECT ON 145mg FENOFIBRATE TABLET



COMPARED WITH LARGER PARTICLES NANOPARTICLE SIZE LEADS TO:[3]

- **Greater solubility**
- **Larger surface area**
- **Increased dissolution velocity**
- **Greater bioavailability**

This was an open label, randomized, single dose, 3 way crossover study. 45 patients (18-41 years) taking fenofibrate 145mg administered with or without meals. Plasma concentrations of fenofibric acid were determined up to 120 hours post-dose. Comparisons were made between fasting and fed conditions.

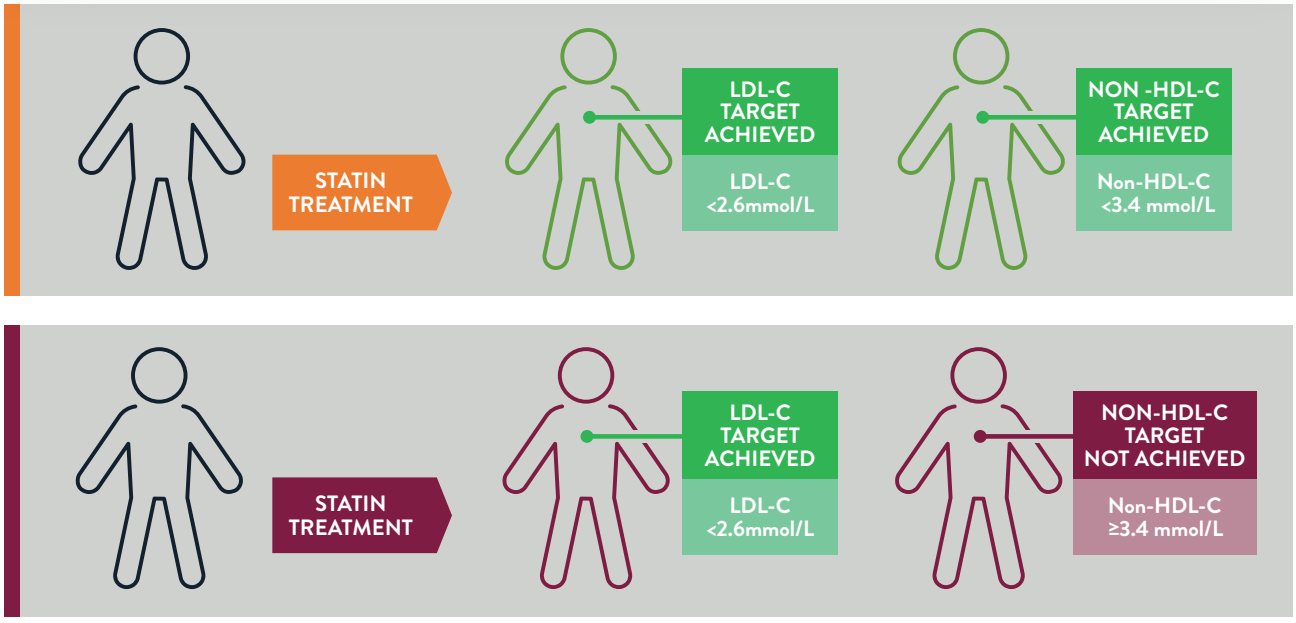
References:
1.Company Core Data Sheet. Fenofibrate. 4th April 2019. 2. Sauron R, Wilkins M, Jessent V et al. Absence of food effect with a 145mg nanoparticle fenofibrate tablet formulation int. J Clin Pharmacol Ther. 2006; 44:64-70.
3. Junghanns H; Muller H. Nanocrystal technology, drug delivery and clinical application. International Journal of Nanomedicine. 2008: 3(3) 296-305.

PATIENT PROFILE

Gender	Male
Age	45 years old
Job	MNC Staff
BMI	28
DISEASE	
Hypertension, Diabetes	
Mixed Dyslipidemia with atherogenic heart disease	
LIPID PROFILE	
TC	3.9 mmol/L
HDL-C	1.0 mmol/L
NON-HDL-C	2.9 mmol/L
TG	3.3 mmol/L
LDL-C	1.4 mmol/L
CURRENT TREATMENT	
Aspirin、Rosuvastatin、Linagliptin、Metformin	

*Patient cases are hypothetical and for illustration purposes only.

Patients who achieve their LDL-C target level may still not achieve their Non-HDL-C target level[1]



LDL-C = Low Density Lipoprotein Cholesterol
HDL-C = High Density Lipoprotein Cholesterol

Meta-analysis of 8 randomized controlled trials involving 62,154 participants.
All trials involved a mean follow up of at least 2 years and more than 1000 patients.

Adapted from Boekholdt SM et al JAMA 2012

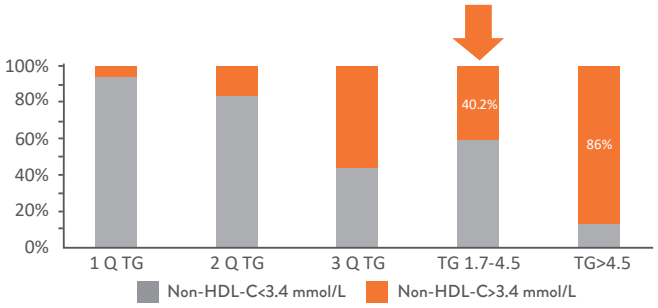
Reference:
1. Boekholdt SM et al. Association of LDL Cholesterol, Non-HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients With Statins. JAMA 2012; 307(12): 1303-1309.

Asian may have higher chance NOT achieve Non-HDL-C target

LDL success rates versus Non-HDL-C success rates by world region in the L-TAP 2 study[1].

Characteristics	All population	Asia	Europe	Latin America	North America
N	9,926	1,949	2,920	988	4,069
LDL-C success and Non-HDL-C success	81.8%	79.2%	86.6%	80.2%	80.2%
LDL-C success and Non-HDL-C failure	18.1%	**20.3%**	13.3%	19.7%	19.7%

Based on TG level, patients Non-HDL-C (>3.4 mmol/L) concentrations despite on-target LDL (≤2.6 mmol/L)[2]



Introduction:

The Lipid Treatment Assessment Project 2 (L-TAP 2) was a multicenter survey of lipid goal attainment in dyslipidemic patients who were on stable lipid-lowering therapy at investigation sites in 9 countries (Canada, Brazil, Mexico, the USA, France, Spain, the Netherlands, South Korea, and Taiwan) between September 2006 and April 2007. This current pre specified analysis of the L-TAP 2 survey describes the attainment of non-HDL-C goals according to the level of risk and compared with LDL-C goal attainment in the whole study population, as well as according to gender, baseline plasma TG levels (≤2.3 mmol/L vs. >2.3 mmol/L), and world region.

Introduction:

In 1590 patients we studied the lipid profile using standard biochemical methods and sequential UC (N = 637) or triglyceride (TG) independent DM (N = 953).

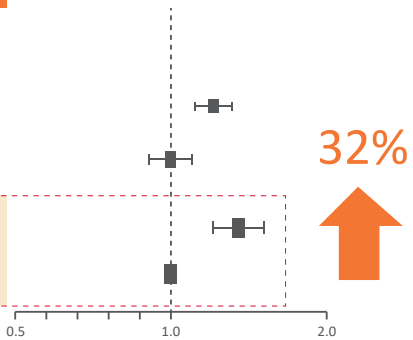
The objective was to assess the number of patients with an indication for lipid-lowering therapy according to their non-HDL cholesterol (N-HDL-C) (>3.4 mmol/L) concentrations despite on-target LDL (≤2.6 mmol/L) values determined using ultracentrifugation (UC) or direct enzymatic methods (DM).

Reference:
1. Santos RD, Waters DD, Tarasenko L, et al. A comparison of non-HDL and LDL cholesterol goal attainment in a large, multinational patient population: The Lipid Treatment Assessment Project 2. Atherosclerosis. 2012;224(1):150-153.
2. Masana L, Ibarretxe D, Heras M, et al. Substituting non-HDL cholesterol with LDL as a guide for lipid-lowering therapy increases the number of patients with indication for therapy. Atherosclerosis. 2013;226(2):471-475.

Patients reaching the LDL-C target but NOT the Non-HDL-C target face a hazard ratio for major CV event of 1.32[1]

Association of LDL, Non-HDL-C, and Apo B with Risk of Cardiovascular Events Among Patients Treated with Statins: A Meta-Analysis.

Target Level		No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
LDL-C	Non-HDL-C			
≥2.6 mmol/L	≥3.4 mmol/L	1877	10419	1.21 (1.13-1.29)
≥2.6 mmol/L	<3.4 mmol/L	467	2873	1.02 (0.92-1.12)
<2.6 mmol/L	≥3.4 mmol/L	283	1435	1.32 (1.17-1.50)
<2.6 mmol/L	<3.4 mmol/L	2760	23426	1.00 (reference)



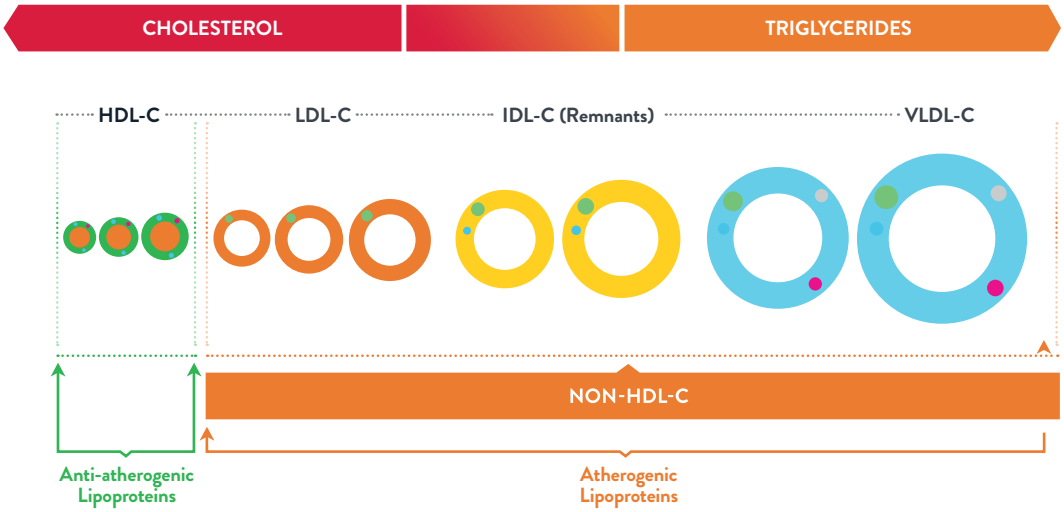
Introduction:

Meta-analysis of 62154 patients enrolled in 8 trials published between 1994 and 2008 from randomized controlled statin trials in which conventional lipids and apolipoproteins were determined in all study participants at baseline and at 1-year follow-up.

Reference:
1.Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: A meta-analysis. JAMA. 2012;307(12):1302-1309.

NON-HDL-C: A recognised secondary target for treatment for CV disease prevention[1]

Non-high-density lipoprotein cholesterol (Non-HDL-C) encompasses all of the atherogenic apolipoprotein B-containing lipoproteins.*[2]



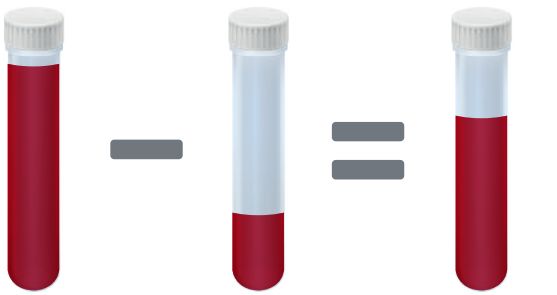
*(LDL-C, very low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, lipoprotein (a), cholymicrons, and their triglyceride (TG)-rich remnants)[5]
CVD = Cardiovascular

This illustration is for representational purposes only

Reference:
1. Mach F., Baigent C., Catapano A. et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European Heart Journal, 2019;00:1-78.
2. Puri R, Nissen SE, Shao M. et al. Non-HDL Cholesterol and Triglycerides Implications for Coronary Atheroma Progression and Clinical Events. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016; 36: 2220-2228.

NON-HDL-C as a secondary target for therapy[1]

Non-HDL-C = Total Cholesterol - HDL-C



LDL-C = TC - HDL-C - (TG / 2.2) mmol/L

LDL-C can be calculated by Friedwald formula. If TG is increasing, the variation of real LDL-C will be enlarged.

LDL-C = Low Density Lipoprotein Cholesterol HDL-C = High Density Lipoprotein Cholesterol
TC = Total Cholesterol TG = Triglyceride

NON-HDL-C AS A SECONDARY TARGET FOR THERAPY

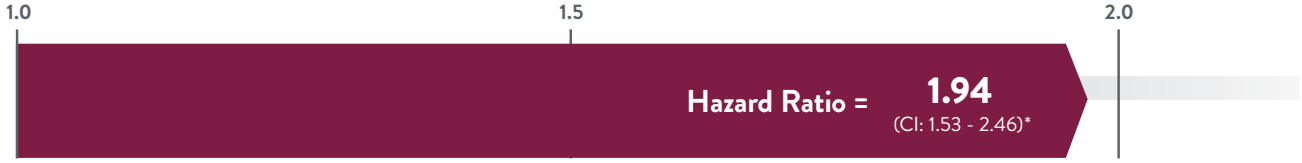
- NON-HDL-C contains: LDL-C, VLDL-C, IDL and CM.
- LDL-C estimation requires measurement of TC, TG and HDL-C in a fasting state. However LDL-C estimation becomes progressively less accurate with increasing TG levels as can occur in patients with diabetes.
- Non-HDL-C estimation has the advantage that it only requires measurement of TC and HDL-C, both of which can be measured reasonably accurately in a non-fasting sample.

Reference:
1.Hirsch GA, Vaid N, Blumenthal RS, et al. Perspectives: The significance of measuring non-HDL-cholesterol. Prev Cardiol. 2002;5(3):156-159.

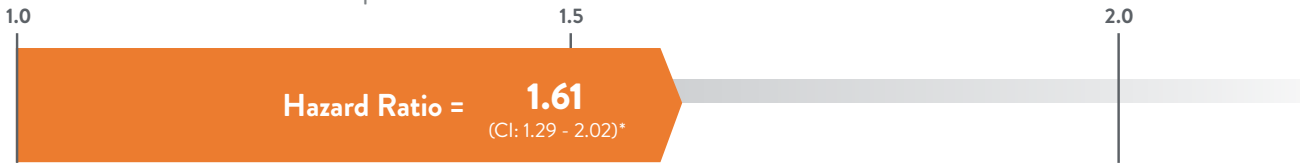
NON-HDL-C is a significant predictor of CVD in diabetic patients[1]

CVD hazard ratios associated with Non-HDL-C and LDL-C

Non-HDL-C > 4.2 mmol/L compared with < 3.3 mmol/L



LDL-C > 3.0 mmol/L compared with < 2.3 mmol/L



Analysis of 2108 individuals aged 45-74 years with diabetes but no CVD at baseline and followed up over an average of 9 years to evaluate the ability of Non-HDL-C and lipoprotein indicators to predict CVD[3]

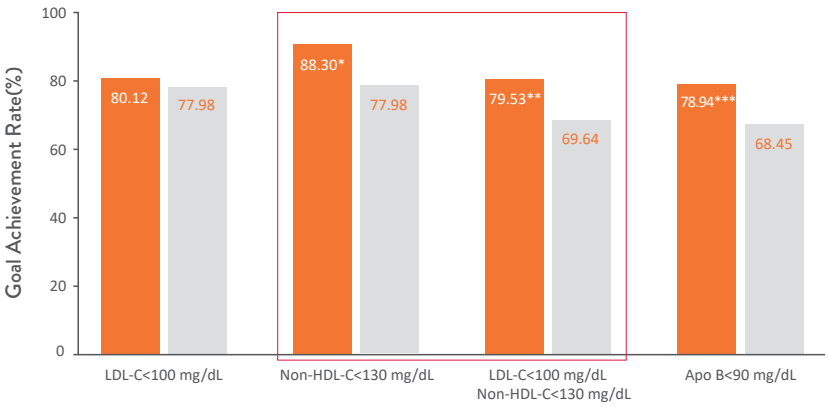
*Highest tertile compared with the lowest tertile
Adapted from Lu W et al. Diabetes Care 2003

Diabetic patients are at high risk for CVD morbidity and mortality which means adequate risk assessment and management is imperative

Reference:
1.Lu W et al. Non-HDL Cholesterol as a Predictor of Cardiovascular Disease in Type 2 Diabetes. Diabetes Care, 2003; 26(1):16-23.

CVD = Cardiovascular Disease

Statin + Fenofibrate can significantly increase the Non-HDL-C goal achievement rate[1]



*p=0.0110 **p=0.0364 ***p=0.0021

Statin

Statin + Fenofibrate

With 8 weeks treatment, co-statin treatment with fenofibrate, Non-HDL-C goal achievement rate is 88.30% (p=0.10110)

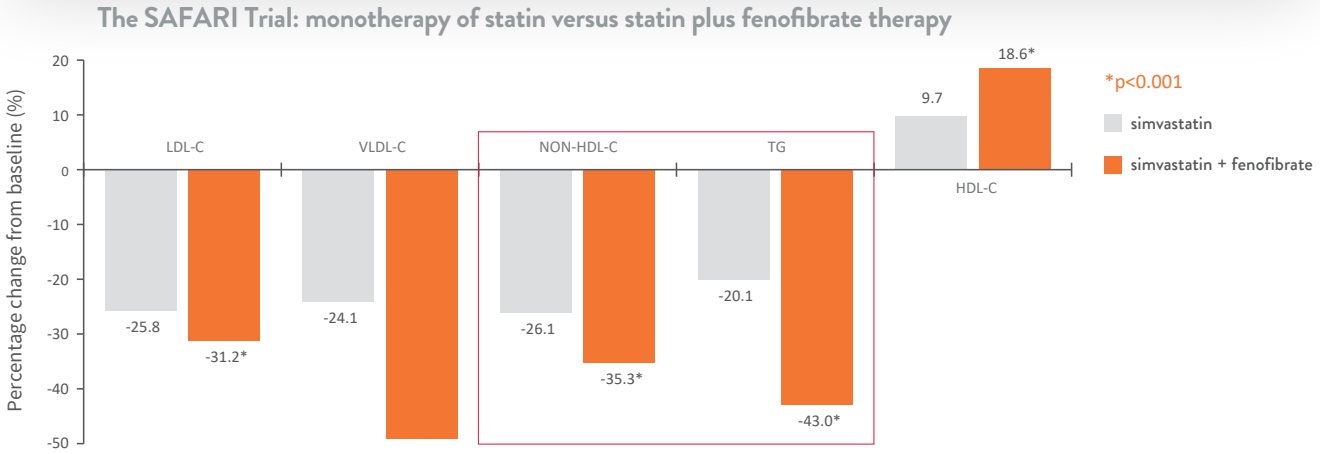
With 8 weeks treatment, co-statin treatment with fenofibrate, Non-HDL-C & LDL-C goal achievement rate is 79.53% (p=0.0364)

Study Design:

This multi-center, randomized, double-blind, parallel-group, therapeutic-confirmatory clinical trial evaluated the efficacy and tolerability of fixed-dose combination therapy with pitavastatin/fenofibrate 2/160 mg in Korean patients with a high risk for CVD and a controlled LDL-C level (<100 mg/dL) and a TG level of 150- 500 mg/dL after a run-in period with pitavastatin 2 mg alone.

Reference:
1.Ihm SH, Chung WB, Lee JM, et al. Efficacy and tolerability of Pitavastatin versus Pitavastatin/Fenofibrate in high-risk Korean patients with mixed dyslipidemia: A multicenter, randomized, double-blinded, parallel, therapeutic confirmatory clinical trial. Clin Ther. 2020;42(10):2021-2035.

A combination of fenofibrate with statin improved all lipid parameters[1]



Study Design:

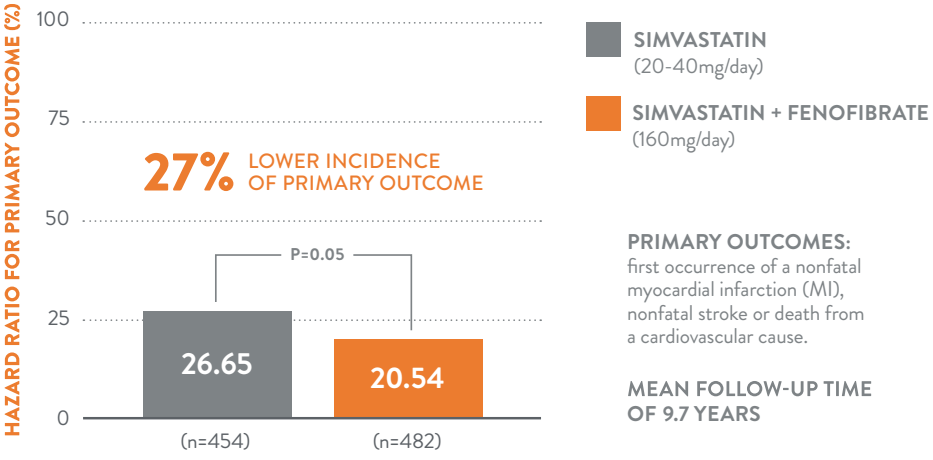
We conducted a multi-center (in the United States), randomized, double-blind, active-controlled, 18-week study to determine if combination therapy with simvastatin plus fenofibrate is more effective in reducing elevated TG levels, thus improving the lipoprotein pattern in patients with combined hyperlipidemia compared with simvastatin monotherapy, and to evaluate safety and tolerability.

Patients (aged 21 to 68 years) with a diagnosis of combined hyperlipidemia (fasting TG levels >150 and <500 mg/dl, and LDL cholesterol >130 mg/dl) received simvastatin monotherapy (20 mg/day, n 207) or simvastatin 20 mg plus fenofibrate (160 mg/day) combination therapy (n 411) for 12 weeks following a 6-week diet and placebo run-in period. From baseline to week 12, median TG levels decreased 43.0% (combination therapy) and 20.1% (simvastatin monotherapy [treatment difference 23.6%, p <0.001]). Mean LDL cholesterol levels decreased 31.2% and 25.8% (treatment difference 5.4%, p <0.001), and high-density lipoprotein cholesterol levels increased 18.6% and 9.7% (treatment difference 8.8%, p <0.001) in the combination therapy versus monotherapy groups, respectively

Reference:
1.Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol. 2005;95(4):462-468.

A statin with fenofibrate reduced the risk of major CV events in dyslipidaemic patients with type 2 diabetes[1]

CVD RISK REDUCTION IN PATIENTS WITH DYSLIPIDAEMIA* AND TYPE 2 DIABETES[8] (POST-TRIAL FOLLOW-UP OF ACCORD LIPID STUDY)



SIMVASTATIN (20-40mg/day)

SIMVASTATIN + FENOFIBRATE (160mg/day)

PRIMARY OUTCOMES: first occurrence of a nonfatal myocardial infarction (MI), nonfatal stroke or death from a cardiovascular cause.

MEAN FOLLOW-UP TIME OF 9.7 YEARS

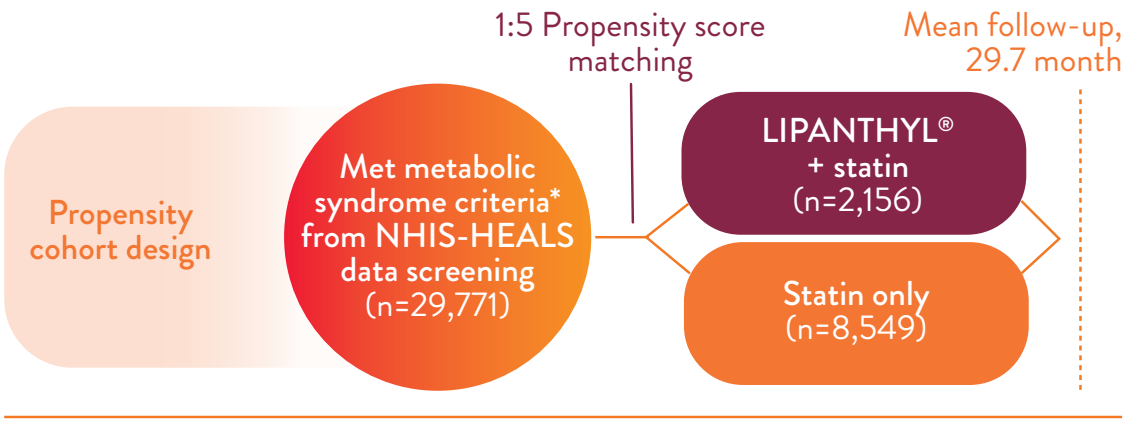
FENOFIBRATE THERAPY WITH A STATIN WAS ASSOCIATED WITH REDUCED CARDIOVASCULAR DISEASE IN STUDY PARTICIPANTS WITH DYSLIPIDAEMIA [8]

*Dyslipidaemia at baseline defined as trigylcerides > 204mg/dl and HDL < 34mg/dl

Adapted from Elam MB et al. JAMA Cardiology 2016

Reference:
1.Elam MB., Ginsberg HN., MD; Lovato LC. et al. Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-TreatedPatients With Type 2 Diabetes. JAMA Cardiology, doi:10.1001/jamacardio.2016.4828. Published online December 28, 2016

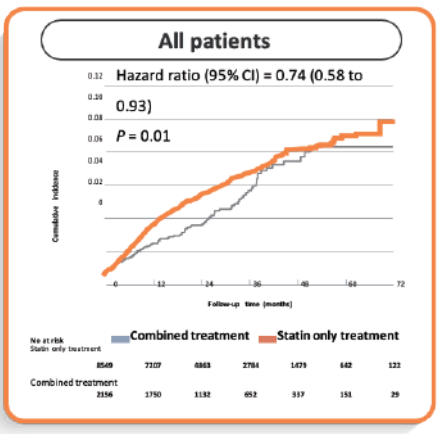
ECLIPSE-REAL demonstrated CV outcomes of LIPANTHYL® add-on therapy among Asian patients with metabolic syndrome in the real-world setting[1]

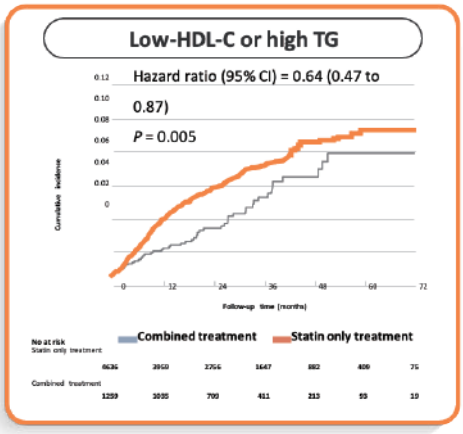


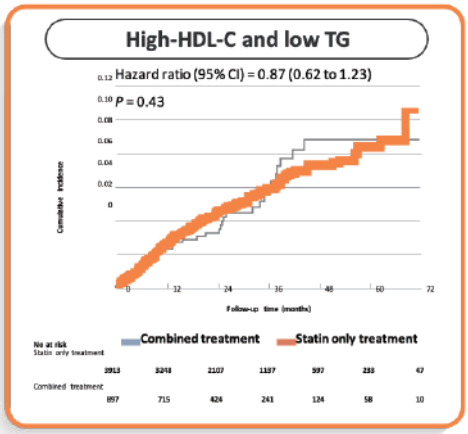
Participants with low-HDL-C or high TG†

Risk of CVD in patients with HDL-C <0.88 mmol/L or TG ≥2.3 mmol/L

Combined treatment with statin and fenofibrate showed better CV risk reduction[1]







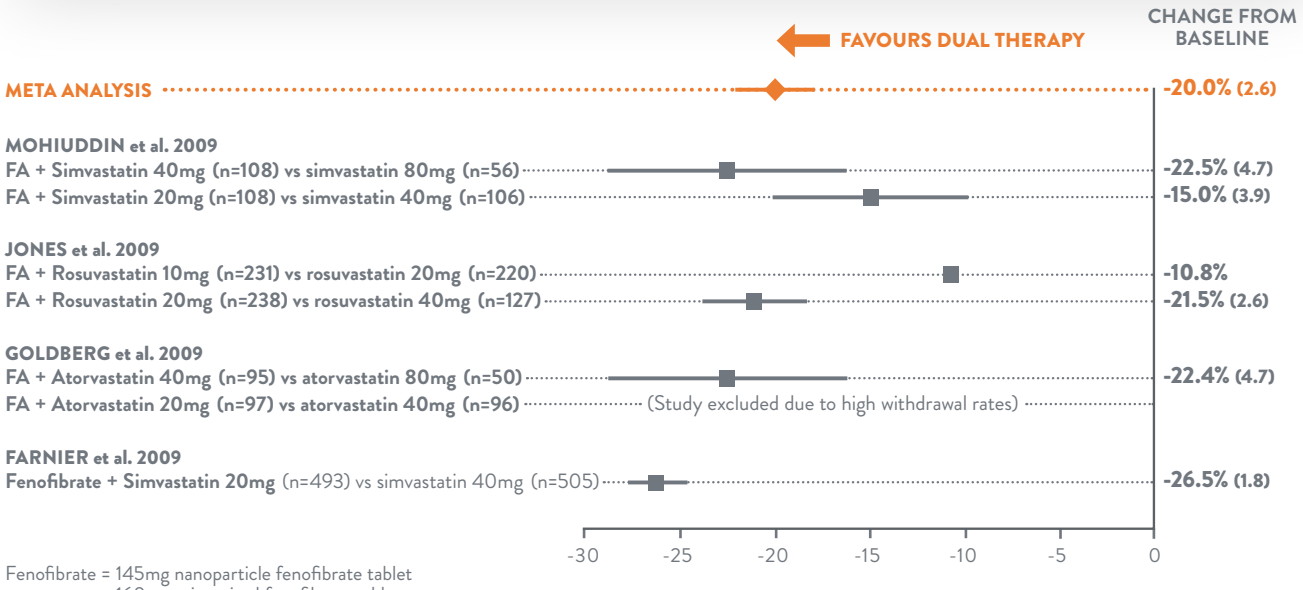
CV risk **26%**, p=0.01

CV risk **36%**, p=0.005

CV risk **13%**, p=0.43

Reference:
1. Kim NH, et al. Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study. BMJ. 2019 Sep 27;366:l5125.

A FIBRATE + STATIN combination lowered triglycerides more effectively than a double dose of statin[1]



Fenofibrate = 145mg nanoparticle fenofibrate tablet
or 160mg micronized fenofibrate tablet
or 200mg micronized capsule
or 300mg non-micronized fenofibrate capsule

FA = 135mg fenofibric acid capsule

Dual therapy versus a double dose of statin forest plot.

Meta-analysis of randomized, double-blind clinical trials comparing fenofibrate plus statin dual therapy with statin monotherapy.

Adapted from Ouwens MJNM et al. Curr Med Res Opin 2015

Reference:
1. Ouwens MJNM. Ansquer J-C. Dreissen S. Systematic literature review and meta-analysis of dual therapy with fenofibrate or fenofibric acid and a statin versus a double or equivalent dose of statin monotherapy. Curr Med Ros Opin 2015; 31: 2273-2285.

No evidence for such a risk [of rhabdomyolysis] was noted in our [ACCORD] study, a finding that was compatible with evidence that fenofibrate, in contrast to gemfibrozil, does not increase plasma concentrations of statins[1,2]

ACCORD LIPID KEY SAFETY RESULTS[1,2]

Type of adverse event	Event	LIPANTHYL® - simvastatin (n=2,765)	Simvastatin (n=2,753)	p value
Muscular*	**Myositis or rhabdomyolysis**	**4 (0.1%)**	**3 (0.1%)**	**NS**
	CPK ever >10x ULN	10 (0.4%)	9 (0.3%)	NS
Renal	End-stage renal disease and dialysis	75 (2.7%)	77 (2.8%)	NS
	Microalbuminuria ≥30 to <300 mg albumin/g creatinine	1,050 (38.2%)	1,137 (41.6%)	0.01
	Macroalbuminuria ≥300 mg albumin/g creatinine	289 (10.5%)	337 (12.3%)	0.04
	Creatinine Women ever >1.3 mg/dL Men ever >1.5 mg/dL	 235 (27.9%) 698 (36.7%)	 157 (18.7%) 350 (18.5%)	 <0.001 <0.001
Hepatic	ALT >3x ULN	52 (1.9%)	40 (1.5%)	NS
	ALT >5x ULN	16 (0.6%)	6 (0.2%)	0.03

Prospective meta-analysis of data from 90 056 individuals in 14 randomised trials of statins was done. Data were obtained on 90 056 participants, of whom 42 131 (47%) had pre-existing CHD, 21 575 (24%) were women, 18686 (21%) had a history of diabetes, and 49 689 (55%) had a history of hypertension. The primary meta-analyses were to be of the effect on clinical outcome in each trial weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of the follow-up and are reported as the effects per 1.0 mmol.L reduction in LDL cholesterol. The main prespecified outcomes were all causes mortality, CHD mortality and non-CHD mortality.

*The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMGCoA reductase inhibitor, especially in case of pre-existing muscular disease. Consequently, the coprescription of fenofibrate with 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 with a close monitoring of potential muscle toxicity.

CPK = creatine phosphokinase; ULN = upper limit of normal; ALT = alanine transaminase

*Company Core Data Sheet. Fenofibrate, Abbott, 22nd February 2021.

Reference:
1. ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med. 2010;362:1563-74.
2. Supplement to: The ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med. 2010;362:1563-74. DOI: 10.1056/NEJMoa1001282.

2016 AHA Statement: statin-fibrate combination therapy is indicated, fenofibrate or fenofibric acid is preferred because of a reduced incidence of DDIs compared with statin-gemfibrozil combination therapy

Recommendations for Statin-Fibrate DDIs

1. When **statin-fibrate combination therapy is indicated, fenofibrate or fenofibric acid is preferred** because of a reduced incidence of DDIs compared with statin-gemfibrozil combination therapy.

2. There are circumstances in which gemfibrozil may be the only available fibrate, cost may be a consideration, or fenofibrate may not be tolerated. Under any circumstance, the use of gemfibrozil should be avoided in combination with lovastatin, pravastatin, and simvastatin.

3. On the basis of pharmacokinetic evidence, the combination of gemfibrozil with lovastatin, pravastatin, and simvastatin is potentially harmful and should be avoided.

Reference:
1.Wiggins BS, Saseen JJ, Page RL 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: A scientific statement from the American Heart Association. Circulation. 2016;134(21):e468-e495.

Fenofibrate showed minor significant pharmacokinetic interactions when tested with several statins [1]

The lack of fenofibrate (fenofibric acid, fenofibric acid glucuronide) effect on statin glucuronidation or the CYP2C8 pathway results in no significant changes in the blood levels of the statin or fenofibric acid if the drugs are administered together.[1]

Major metabolic pathway	Fenofibrate	Statin	Gemfibrozil
Glucuronidation	UGT1A9 & 2B7	UGT1A1 & 1A3 with most of statin	UGT1A1 & 1A3
Effect on oxidative metabolism	CYP2C9 mild-to-moderate inhibitor	metabolism via CYP 2C9 isoenzymes Atovastatin & Rosuvastatin	CYP2C9 Strong inhibitor
	CYP2C19、2A6 mild inhibitor	metabolism via CYP 2C8 isoenzymes Simvastatin	CYP2C8 Strong inhibitor

Reference:
1.Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: Evaluating the risks of pharmacokinetic drug interactions. Expert Opin Drug Saf. 2006;5(1):145-156.

2019 ESC/EAS guidelines for the management of dyslipidaemias recommend the following target lipid levels [1,2]

- The targeted approach to lipid management is primarily aimed at reducing LDL-C.[1,2]
- Non-HDL-C evaluation recommended for risk assessment, particularly in people with high triglyceride levels, diabetes mellitus, obesity or very low LDL-C levels.[1,2]

CVD risk	LDL-C Target Levels	Non-HDL-C Target Levels
Very high risk*	LDL-C <1.4 mmol/L (<55 mg/dL)	<2.2 mmol/L (< 85 mg/dL)
High risk	LDL-C <1.8 mmol/L (<70 mg/dL)	< 2.6 mmol/L (< 100 mg/dL)
Moderate risk	LDL-C <2.6 mmol/L (<100 mg/dL)	<3.4 mmol/L (< 130 mg/dL)
Low risk	LDL-C <3.0 mmol/L (<116 mg/dL)	

*This target LDL-C also applies to patients with established atherosclerotic cardiovascular disease, as per the ESC Guidelines on cardiovascular disease prevention in clinical practice.[2]

References:
1. Mach F, Baigent C, Catapano AL, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–188.
2. Visseren FLJ, Mach F, Smulders YM, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–3337.

2020 AACE/ACE Guideline Treatment Algorithm on Dyslipidemia for Diabetic Patients[1]

Risk category	Risk factors / 10-year risk	Treatment goals		
		LDL-C (mmol/L)	Non-HDL-C (mmol/L)	Apo B (mmol/L)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<1.4	<2.0	<1.8
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid, or peripheral vascular disease – Diabetes or CKD 3/4 with one or more risk factor(s) – HeFH	<1.8	<2.6	<2.0
High risk	≥2 risk factors and 10-year risk >10% or CHD risk equivalentc, including diabetes or CKD 3/4 with no other risk factors	<2.6	<3.4	<2.3
Moderate risk	≥2 risk factors and 10-year risk <10%	<3.4	<4.1	NR
Low risk	≤1 risk factor	<4.1	<4.9	NR

Reference:
1.Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, Blonde L, Bush MA, DeFronzo RA, Garber JR, Garvey WT, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Perreault L, Rosenblit PD, Samson S, Umpierrez GE. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY. Endocr Pract. 2020 Jan;26(1):107-139. doi: 10.4158/CS-2019-0472. PMID: 32022600.

NON-HDL-C: A CLINICAL CHALLENGE...

- Non-HDL-C is a recognised secondary target for the treatment of residual CV risk[1]
- Despite statin monotherapy patients can remain at substantial CV risk[2]

WHEN COMPARED WITH A STATIN ALONE

- Offers additional control in atherogenic dyslipidaemia[3,4]
- Lipanthyl in combination with a statin reduced Non-HDL-C[3]
- Lipanthyl in combination with a statin reduced risk of major CV events in patients with dyslipidaemia and Type 2 diabetes[4]

A STATIN + LIPANTHYL® FENOFIBRATE

YOUR FORMULA FOR SUCCESS

IN ATHEROGENIC DYSLIPIDAEMIA[3,4]

THE WORLD'S **NO. 1 FIBRATE**[5]

References:
1. Hirsch GA, Vaid N and Blumenthal RS. The significance of measuring Non-HDL-Cholesterol. Preventive Cardiology, 2002; 5:156-159.
2. Cholesterol Treatment Trialists' (CTT) Collaborators. Baigent C, Keech A, Kearny PM et al. Efficacy and safety of cholesterollowering treatments: prospective a meta-analysis of data from90 056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267-1278.
3. Grundy SM, Vega G, Yuan Z et al. Effectiveness and Tolerability of Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (The SAFARI Trial). Am J Cardial. 2005; 95: 462-468.
4. Elam MB., Ginsberg HN., MD; Lovato LC. et al. Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-TreatedPatients With Type 2 Diabetes. JAMA Cardiology, doi:10.1001/jamacardio.2016.4828. Published online December 28, 2016
5. IQVIA MIDAS database Q2 2022.
image: Freepik.com

LIPANTHYL PENTA 145

1. NAME OF THE MEDICINAL PRODUCT
LIPANTHYL® PENTA 145, Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 145.0 mg fenofibrate as nanoparticles.
Excipients with known effect:
Each film-coated tablet contains:
- 132.00 mg lactose monohydrate
- 145.00 mg sucrose
- 0.50 mg soybean lecithin

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
White, oblong, film-coated tablets engraved "145" on one side and the "F" logo on the other side.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
LIPANTHYL® PENTA 145 is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following conditions:
- Severe hypertriglyceridemia with or without low HDL cholesterol
- Mixed hyperlipidemia when a statin is contraindicated or not tolerated
- Mixed hyperlipidemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled

4.2. Posology and method of administration
The diet should be continued during treatment with this medicinal product. Response to treatment should be monitored by recording serum lipid levels. If an adequate lipid-lowering response has not been achieved after several months of treatment with fenofibrate (e.g. 3 months), complementary or different therapeutic measures should be considered.

Posology:
Adults:
Recommended daily dose: 1 film-coated tablet (containing 145 mg fenofibrate) daily.

Patients currently taking fenofibrate 200 mg or 160 mg once daily can be changed to LIPANTHYL® PENTA 145 (1 film-coated tablet daily) without further dose adjustment.

Elderly patients (> 65 years old):
No dose adjustment is necessary. The usual dose is recommended except for decreased renal function with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² (see "Patients with renal impairment")

Patients with renal impairment:
Fenofibrate should not be used if severe renal impairment, defined as eGFR < 30 ml/min/1.73 m², is present.
If eGFR is between 30 and 59 ml/min/1.73 m², the daily dose should not exceed 100 mg fenofibrate (standard) or 67 mg micronised.
If, during follow-up, the eGFR decreases persistently to < 30 ml/min/1.73 m², fenofibrate should be discontinued.

Hepatic impairment:
LIPANTHYL® PENTA 145 is not recommended for patients with hepatic impairment due to the lack of data.

Children and adolescents:
The safety and efficacy of fenofibrate have not been sufficiently established in children and adolescents below the age of 18. No studies are available. Therefore, the use of fenofibrate is not recommended in children and adolescents under 18 years.

Method of administration:
The medicinal product may be given at any time of the day, with or without food (see Section 5.2).
The film-coated tablet should be swallowed whole with a glass of water

4.3. Contraindications
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality)
- Known gallbladder disease
- Severe renal insufficiency (estimated glomerular filtration rate < 30 ml/min/1.73 m²)
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

LIPANTHYL® PENTA 145 should not be taken by patients allergic to peanuts, arachis oil, soya lecithin (3-sn-phosphatidyl choline) or related products due to the risk of hypersensitivity reactions.

4.4. Special warnings and precautions for use
Secondary cause of hypercholesterolemia such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease or alcoholism should be treated before LIPANTHYL® PENTA 145 therapy is considered.

Secondary causes of hyperlipidaemia may occur during pharmacological treatment with diuretics, beta-blockers, oestrogens, gestagens, combined oral contraceptives, immunosuppressants and protease inhibitors. In these cases, tests should be carried out to establish whether primary or secondary hyperlipidaemia is involved (these medicinal products may trigger a rise in lipid values).

Liver:
As with other lipid-lowering drugs, increases have been reported in transaminase levels in some patients whilst taking fenofibrate. In the majority of the observed cases, the elevations were temporary, minor and asymptomatic. It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and regularly thereafter.
Patients displaying elevated transaminase levels should be closely monitored. Treatment should be discontinued if ASAT (SGOT) and ALAT (SGPT) levels increase to more than 3 times the upper limit of normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.

Pancreas:
Pancreatitis has been reported in patients taking fenofibrate (see Sections 4.3 and 4.8). In patients with severe hypertriglyceridemia, this may be due to insufficient efficacy of the medicinal product, a direct drug effect or a secondary phenomenon mediated through cholelithiasis with obstruction of the common bile duct.

Muscle:
Muscle toxicity including rare cases of rhabdomyolysis, with or without renal failure, has been reported with the administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in case of hypoalbuminaemia and previous renal insufficiency.

Patients with predisposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or family history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at increased risk of developing rhabdomyolysis. For these patients, the benefits and risks of fenofibrate therapy should be carefully weighed up.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/ or marked increases in creatine phosphokinase (CPK) (levels exceeding five times the upper normal range). In such cases, the medicinal product should be stopped.

The risk of muscle toxicity may be elevated if this medicinal product is combined with another fibrate or with an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscle disease. Consequently, the combination of fenofibrate with an HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined hyperlipidemia and high cardiovascular risk without any history of muscle disease and with close monitoring of potential muscle toxicity.

Renal function:
LIPANTHYL® PENTA 145 is contraindicated in severe renal impairment (see Section 4.3).
LIPANTHYL® PENTA 145 should be used with caution in patients with mild to moderate renal insufficiency. Dose adjustment is required in patients with an eGFR between 30 and 59 ml/min/1.73 m² (see Section 4.2).
Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable over time with no evidence of continued increase with long-term therapy. A return to baseline values was observed following discontinuation of treatment.
During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 µmol with co-administered fenofibrate and simvastatin versus 4.4% with statin monotherapy. 0.3% of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 µmol/l.

Treatment should be interrupted when the creatinine levels is 50% above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter.

Excipients:
This medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials (the ACCORD lipid trial and FIELD study) in patients with type 2 diabetes mellitus.

4.5. Interactions with other medicinal products and other forms of interaction
Oral anticoagulants:
Fenofibrate may enhance the oral anticoagulant effect and thus may increase the risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted – if necessary – whilst monitoring coagulation parameters (International Normalized Ratio).

HMG-CoA reductase inhibitors and other fibrates:
The risk of serious muscle damage is increased if fenofibrate is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution, and patients monitored for signs of muscle damage (see Section 4.4).

Ciclosporine:
Isolated cases of severe albeit reversible, impairment of renal function have been reported during concomitant administration of fibrate-containing medicinal products and ciclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate discontinued in the case of significant changes in diagnostic laboratory parameters.

Glitazones:
Some cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL-cholesterol if one of these components is added to the other. Either therapy should be discontinued if HDL cholesterol is too low.

Cytochrome P450 enzymes:
In-vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1 or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and moderate inhibitors of CYP2C9 at therapeutic concentrations.

Patients coadministered fenofibrate and CYP2C19, CYP2A6 and especially CYP2C9 metabolised drugs with a narrow therapeutic index, should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

4.6. Pregnancy and Lactation

Pregnancy:
There are no adequate data on the use of fenofibrate during pregnancy. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects were observed at doses in the range of maternal toxicity (see Section 5.3). The potential risk for humans is unknown. Therefore, LIPANTHYL® PENTA 145 should only be used during pregnancy after a careful benefit/risk assessment.

Lactation:
It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Consequently, LIPANTHYL® PENTA 145 should not be used during breast-feeding.

Fertility:
Reversible effects on fertility have been observed in animal studies (see Section 5.3).
There are no clinical data on fertility from the use of LIPANTHYL® PENTA 145.

4.7. Effect s on the ability to drive and use machines
LIPANTHYL® PENTA 145 has no or negligible effect on the ability to drive and use machines.

4.8. Undesirable effects
The most commonly reported adverse effects during fenofibrate therapy are digestive or gastrointestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (n=2344) and post-marketing* with the frequencies indicated below:

MedDRA system organ class	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1,000, < 1/100)	Rare (≥ 1/10,000, < 1/1,000)	Frequencies unknown (cannot be estimated from the available data)
Blood and lymphatic system disorders			Haemoglobin decreased White blood cell count decreased	
Immune system disorders			Hypersensitivity	
Nervous system disorders		Headache		
Vascular disorders		Thromboembolism (i.e. pulmonary embolism, deep vein thrombosis)*		
Respiratory tract, thoracic and mediastinal disorders				Interstitial pulmonary diseases
Gastrointestinal tract disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhea, flatulence)	Pancreatitis*		
Hepatobiliary disorders	Transaminases increased (see Section 4.4)	Cholelithiasis (see Section 4.4)	Hepatitis	Jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic)
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g. rashes, pruritus, urticaria)	Alopecia Photosensitivity	Severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
Musculoskeletal, connective tissue and bone disorders		Muscle disorders (e.g. myalgia, myositis, muscular spasms and weakness)		Rhabdomyolysis
Reproductive system and breast disorders		Sexual dysfunction		
General disorders and administration site conditions			Fatigue	
Investigations	Blood homocysteine level increased**	Blood creatinine increased	Blood urea increased	

* In the FIELD study, a randomized placebo-controlled clinical trial performed in 9795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022) and a statistically non-significant increase in deep vein thrombosis (placebo 1.0% [48/4900 patients] versus fenofibrate 1.4% [67/4895 patients]; p = 0.074).

** In the FIELD study, the average increase in blood homocysteine levels in treated patients was 6.5 µmol/l, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance is unclear.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Drug Office, Department of Health. Website: http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/adr_reporting/index.html

4.9. Overdose
Only isolated reports of fenofibrate overdose have been received to date. In the majority of cases no overdose symptoms were reported. There is no specific antidote. If an overdose is suspected, symptomatic treatment should be initiated and suitable supportive measures taken. Fenofibrate cannot be eliminated by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: lipid lowering agents/cholesterol and triglyceride lowering products/fibrates

ATC code: C10AB05

Fenofibrate is a fibric acid derivative whose lipid-regulating effects in humans are mediated via activation of PPARα (peroxisome proliferator activated receptor type alpha).

Activation of PPARα increases the activity of lipoprotein lipase and reduces the production of apolipprotein CIII. Via this mechanism, fenofibrate raises lipolysis and elimination of atherogenic triglyceride-rich particles from the plasma. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

The above-mentioned effects of fenofibrate lead to a reduction in very-low-density and low-density lipoproteins (VLDL and LDL) containing apolipoprotein B and an increase in the high-density lipoproteins (HDL) due to increased production of apoproteins AI and AII.

Patients with an elevated CHD (coronary heart disease) risk commonly express an atherogenic lipoprotein phenotype characterized by an increased fraction of small dense LDL particles. By regulating the synthesis and catabolism of VLDL, fenofibrate lowers the levels of small dense LDL and increases LDL clearance.

During clinical trials with fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%.

In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol (LDL, HDL) results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or apo B to apo AI, all of which are markers of atherogenic risk.

There is evidence that treatment with fibrates may reduce coronary heart disease events but it has not been shown to decrease all-cause mortality in the primary or secondary prevention of cardiovascular disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study in 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Treatment with fenofibrate plus simvastatin did not show significant differences in the composite primary endpoint of non-fatal myocardial infarction, non-fatal stroke and cardiovascular deaths compared to simvastatin monotherapy (hazard ratio [HR] 0.92; 95% CI: 0.79 to 1.08; p = 0.32; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidemic patients, defined as those in the lowest tertile of HDL-C (≤ 34 mg/dL or 0.88 mmol/L) and highest tertile of TG (≥ 204 mg/dL or 2.3 mmol/L), fenofibrate plus simvastatin therapy demonstrated a 31% relative risk reduction compared to simvastatin monotherapy for the composite primary outcome criterion (Hazard Ratio [HR] 0.69; 95% CI 0.49 to 0.97; p = 0.03; absolute risk reduction: 4.95%). Another pre-specified subgroup analysis identified a statistically significant treatment-by-gender interaction (p = 0.01) indicating a possible treatment benefit of combination therapy in men (p = 0.037) but a potentially higher risk for the primary endpoint in women treated with combination therapy compared to simvastatin monotherapy (p = 0.069). This was not observed in the above-mentioned subgroup of patients with dyslipidemia, but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

Extravascular deposits of cholesterol (tendinous and tuberous xanthomas) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

In patients with elevated baseline Lp(a) or fibrinogen levels, treatment with fenofibrate produced a significant lowering of Lp(a) or fibrinogen concentrations. Other inflammatory markers such as C-reactive protein are reduced with fenofibrate treatment.

Fenofibrate produces an approximately 25% reduction of uric acid levels. This is of additional benefit in dyslipidaemic patients with hyperuricaemia.
In animal studies and a clinical trial, fenofibrate inhibited platelet aggregation induced by ADP, arachidonic acid and epinephrine.

5.2. Pharmacokinetic properties
LIPANTHYL® PENTA 145 contains 145 mg of fenofibrate as nanoparticles in the form of a film-coated tablet.

Absorption:
Maximum plasma concentrations (C_{max}) occur within 2 - 4 hours after oral administration. Plasma concentrations remain constant in any given individual following repeated administration.

Contrarily to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of the nanoparticle formation is independent from food intake. Therefore, the medicinal product may be taken without regard to meals.

A study involving healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and C_{max}) to fenofibric acid is not affected by food.

Distribution:
Fenofibric acid is strongly bound to plasma albumin > 99%).

Metabolism and excretion:
After oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP3A4. No hepatic microsomal metabolism is involved.

The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. Plasma clearance of fenofibric acid is unchanged in the elderly patients.

Pharmacokinetic studies with single and repeated dosing have demonstrated that the active substance does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

The plasma elimination half-life of fenofibric acid is approximately 20 hours.

5.3. Preclinical safety data
In a three-month, oral, non-clinical study in rats with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I fibres) and heart failure, anaemia and decreased body weight were seen. No skeletal toxicity was noted at doses up to 30 mg/kg (approximately 17 times the maximum recommended human dose (MRHD)). No signs of cardiac toxicity were noted at approximately three times the MRHD.
Reversible ulcers and erosions in the gastrointestinal tract occurred in dogs treated for three months. No gastrointestinal lesions were noted in this study at approximately five times the MRHD.

Studies on mutagenicity of fenofibrate have been negative.
In rats and mice, liver tumors have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in humans.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses. Reversible hypospermia, testicular vasculation and immaturity of the ovaries were observed in a repeat-dose study with fenofibric acid in young dogs. However, no effect on fertility were detected in preclinical reproductive studies with fenofibrate.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
Core:
Sucrose, Lactose monohydrate, microcrystalline cellulose and colloidal silica anhydrous,
Crospovidone, Hypromellose, Sodium lauril sulfate, Docusate sodium, Magnesium stearate.
Coating:
Polyvinyl alcohol, Titanium dioxide (E171), Talc, Soybean lecithin, Xanthan gum,

6.2. Incompatibilities
Not applicable.

6.3. Shelf-life
3 years

6.4. Special precautions for storage
Store in the original package, at a temperature not exceeding 30°C.

6.5. Nature and contents of container
Thermoformed blister strips (clear PVC/PE/ PVDC sealed with aluminum complex)
Box of 30 tablets.

6.6. Instructions for use and handling
No special requirements.

6.7. Date of last revision
Jan 2019
Version: SOLID10003190760v6.0

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