For patients with primary or mixed hypercholesterolemia

Choose ATOZET® for the power to help take LDL-C lower

- Powerful **dual action** to **help lower LDL-C** in patients with hypercholesterolemia and **reduce CV events** in patients with CHD and a history of acute coronary syndrome[11]
- **ATOZET®** provided **53% mean LDL-C reduction** at the lowest dose (10/10mg) - similar to the highest dose of *atorvastatin* (80mg, 54%)[7]
- **ATOZET®** provided **significantly greater mean additional LDL-C reduction** vs. doubling dose of atorvastatin or switching to *rosuvastatin* [8,9]
- **ATOZET®** was **generally well tolerated** in multiple clinical trials[12]

Before prescribing ATOZET®, please read the prescribing information .

MSD

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EZETROL® Atozet® (ezetimibe and atorvastatin) tablets

HK-ATO-00033 12/19

Think beyond monotherapy

ACHIEVE TARGET LDL-C LEVELS WITH POWERFUL DUAL ACTION OF

ATOZET®

IMPROVE-IT OUTCOMES RESULTS[1]

MSD

2019 ESC/EAS Guidelines for the Management of Dyslipidaemia[1]

Recommended LDL-C goals for very-high-risk and high-risk patients[1]

Very-high-risk patients include

- DM with target organ damage (microalbuminuria, retinopathy, or neuropathy), OR *at least* **three** major risk factors, OR early onset of T1DM >20 years
- FH with ASCVD or with another risk factor
- Severe CKD
- Documented ASCVD
- Calculated 10-year risk SCORE of ≥10%

Achieve LDL-C goal **<1.4 mmol/L** AND at least **50%** reduction in LDL-C from baseline*[1]

High-risk patients include

- DM without target organ damage, with DM duration ≥10 years or another risk factor
- Patients with FH without other major risk factors
- Moderate CKD
- Markedly elevated single risk factors (**TC > 8mmol/L** OR **LDL-C > 4.9mmol/L**), OR **BP > 180/110mmHg**
- Calculated 10-year risk SCORE of ≥5% or <10%

Achieve LDL-C goal **<1.8 mmol/L** AND at least **50%** reduction in LDL-C from baseline*[1]

*The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

Combination therapy may be needed to reach LDL-C goal

2019 AACE/ACE Consensus Statement[2]

AACE Lipid targets for patients with Type II Diabetes[2]

Extreme risk	Patients with DM plus established clinical CVD	**Target LDL-C goal: <1.4mmol/L**
Very high risk	Patients with DM and major ASCVD risks	**Target LDL-C goal: <1.8mmol/L**
High risk	DM but no other major risk and/or age <40	**Target LDL-C goal: <2.6mmol/L**

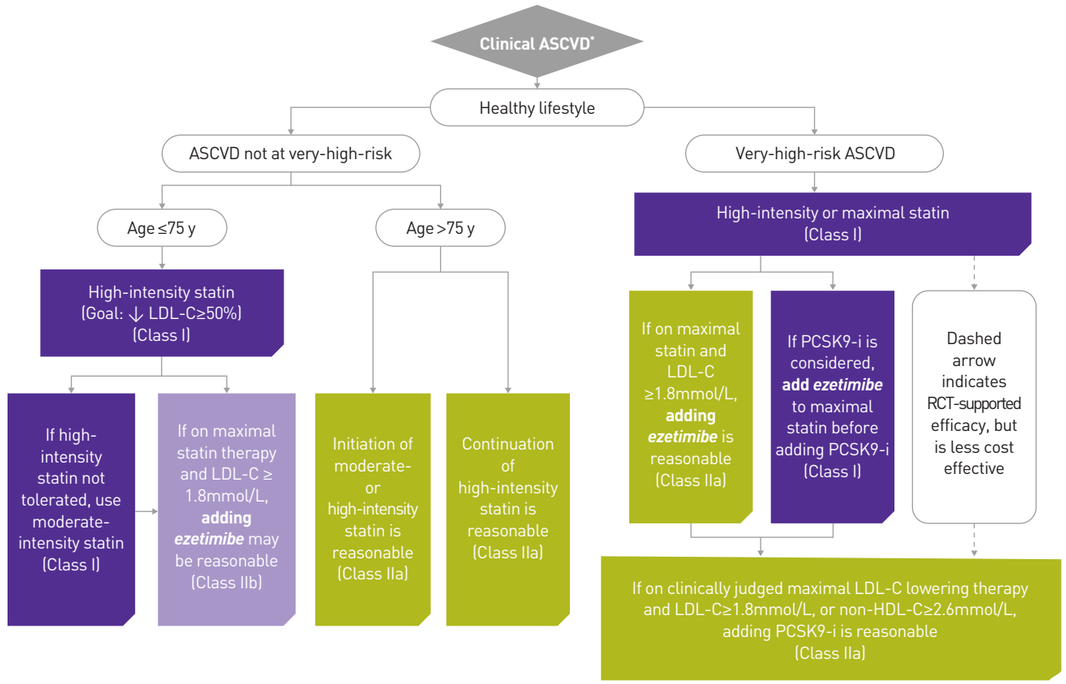
Abbreviations: AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology; ASCVD=atherosclerotic cardiovascular disease; BP=blood pressure; CKD=chronic kidney disease; CVD=cardiovascular disease; DM=diabetes mellitus; EAS=European Atherosclerosis Society; ESC=European Society of Cardiology; FH=familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; SCORE=Systematic Coronary Risk Estimation; TC=total cholesterol; T1DM=Type 1 diabetes mellitus

INTERNATIONAL GUIDELINES

2018 AHA/ACC Guideline on the Management of Blood Cholesterol[3]

AHA/ACC guideline recommends to use *ezetimibe* as second-line therapy in association with statins if LDL-C levels continue to exceed ≥1.8mmol/L.[3]

Secondary prevention in patients with clinical ASCVD[3]



*Clinical ASCVD consists of ACS, those with history of MI, stable or unstable angina or coronary other arterial revascularization, stroke, TIA, or PAD including aortic aneurysm, all of atherosclerotic origin

Very-high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.[3]

Major ASCVD events	High-risk conditions
Recent ACS (within the past 12 months)	Age ≥65 years old
History of MI (other than recent ACS event listed above)	Heterozygous FH
History of ischemic stroke	History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Symptomatic PAD	DM
	Hypertension
	CKD (eGFR 15-59mL/min/1.73m^2)
	Current smoking
	Persistently elevated LDL-C (≥2.6mmol/L) despite maximally tolerated statin therapy and *ezetimibe*
	History of congestive HF

Abbreviations: ACC=American College of Cardiology; ACS=acute coronary syndrome; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate; FH=familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; HF=heart failure; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PAD=peripheral artery disease; PCSK9-i=proprotein convertase subtilisin/kexin type 9 inhibitor; RCT=randomized controlled trial; TIA=transient ischemic attack

Treatment gap in dyslipidaemia management

DYSIS II: a multinational, multicenter, observational study of lipid profiles, lipid target value attainment, and LLT of 10,661 patients with stable CHD or being hospitalized for an ACS event in 18 countries[4]

About 2 in 3 patients did not reach their recommended LDL-C levels of <1.8mmol/L[4]

In CHD patients[4]

(n=6,794), mean baseline LDL-C was 2.27mmol/L

About **70.6%** of patients did not reach their LDL-C goal, with a median distance of **0.62mmol/L from LDL-C goal**

93.8% (n=6,370) were on LLT, of which **82.3% were on statin monotherapy**

Mean LLT-treated LDL-C baseline was 2.22mmol/L

In ACS patients[4]

(n=3,867), mean baseline LDL-C was 2.80mmol/L

About **81.1%** of patients did not reach their LDL-C goal, with a median distance of **1.11mmol/L from LDL-C goal**

65.2% (n=2,521) were on LLT, of which **90.4% were on statin monotherapy**

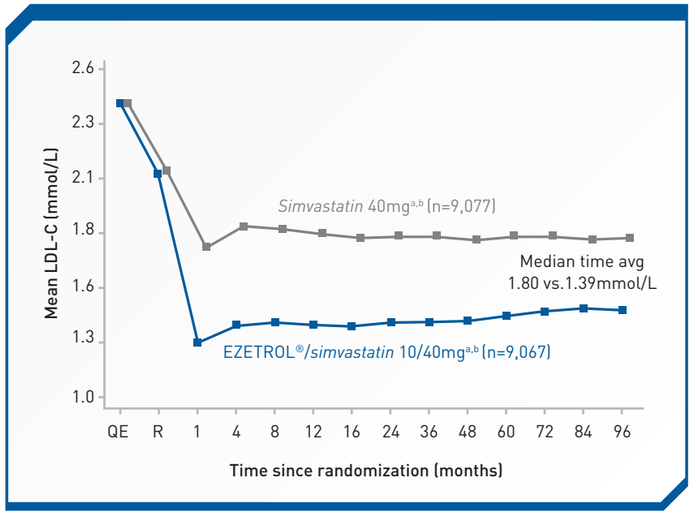
Mean LLT-treated LDL-C baseline was 2.51mmol/L

Study design: The DYSIS II study aimed to determine LDL-C target value attainment, use of LLT, and cardiovascular outcomes in patients with stable CHD and those suffering from ACS. The study included 10,661 patients from 18 countries. Patients with either stable CHD or an ACS were enrolled if they were ≥18 years old and had a full lipid profile available. Data were collected at a physician visit (CHD cohort) or at hospital admission and 120 days later (ACS cohort).[4]

Abbreviations: ACS=acute coronary syndrome; CHD=coronary heart disease; DYSIS=Dyslipidemia International Study; LDL-C=low-density lipoprotein cholesterol; LLT=lipid lowering therapy

IMPROVE-IT: A trial of 18,144 patients with high-risk ACS

Powerful LDL-C reductions with EZETROL® + statin combination therapy[5,6]

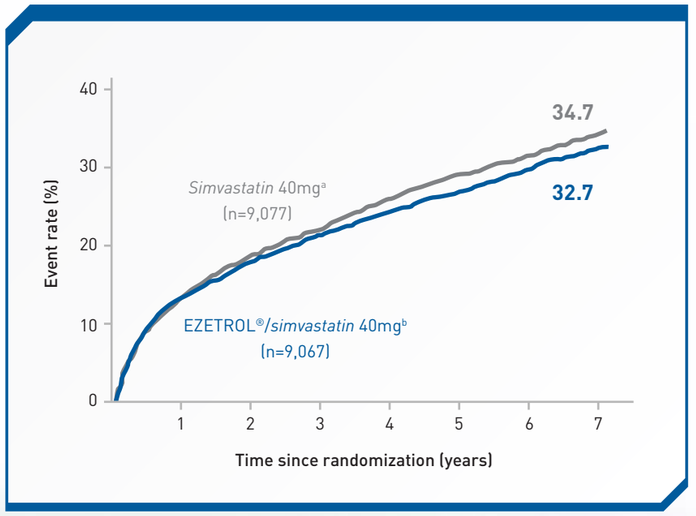


Compared to statin monotherapy, **EZETROL® add-on therapy reduced LDL-C by 24% with NNT=50**[5,6]

24% LDL-C reduction vs *simvastatin* 40mg at 1 year (*p<0.001*)

[a] 27% of patients on *simvastatin* 40mg were uptitrated to the 80mg dose; 6% on **EZETROL®** */simvastatin* 10/40mg were uptitrated to the 10/80mg dose.
[b] Mean baseline LDL-C was 2.4mmol/L in both treatment groups.

Primary endpoint: **Significant reductions in major CV events** with **EZETROL®** + statin combination therapy compared with *simvastatin* alone at 7 years[5,6]



6.4% RRR in major CV events at 7 years
HR=0.936 (95% CI: 0.89-0.99); *p=0.016*

[a] 27% of patients were uptitrated to *simvastatin* 80mg.
[b] 6% were uptitrated to EZETROL®/*simvastatin* 10/80mg.

Reduction in both non-fatal MI (13% RRR with *p*=0.002**) and non-fatal stroke (20% RRR** with *p*=0.010**)** vs. *simvastatin* alone with **EZETROL®** + statin combination were shown in IMPROVE-IT[5,10]

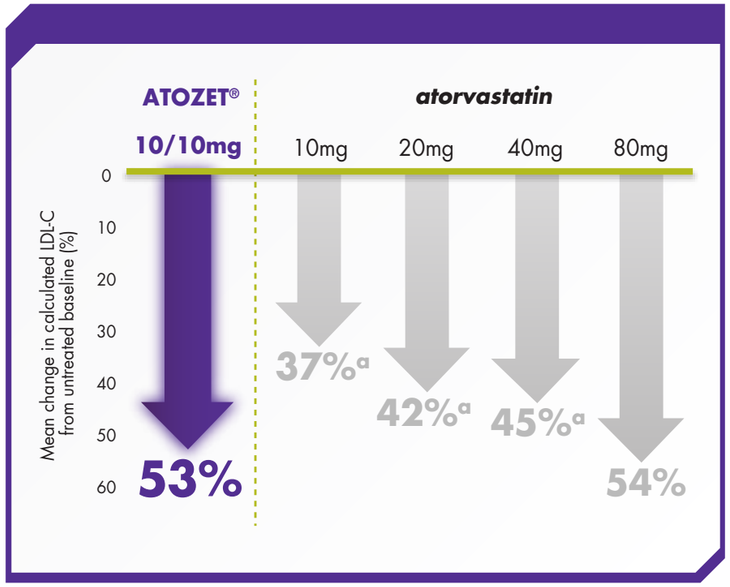
Study design: The IMPROVE-IT was a double-blind, randomized study involving 18,144 patients who had been hospitalized for an ACS within the preceding 10 days and had LDL-C levels of 1.3-2.6mmol/L if they were receiving LLT or 1.3-3.2mmol/L if they were not receiving LLT. The combination of *simvastatin* (40mg) and *ezetimibe* (10mg) was compared with *simvastatin* (40mg) alone and placebo. The primary end point was a composite of CV death, non-fatal MI, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or non-fatal stroke. The median follow-up was 6 years.[5]

Abbreviations: ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; IMPROVE-IT=Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; MI=myocardial infarction; NNT=number needed to treat; RRR=relative risk reduction

In a clinical study of patients with hyperlipidemia and not on lipid-lowering therapy,

ATOZET® 10/10mg powerfully lowered mean LDL-C by 53%[7]

Efficacy of the lowest dose of ATOZET® (10/10mg) was similar to that the highest dose of *atorvastatin* (80mg)[7]



Mean pooled untreated baseline calculated LDL-C was 4.70mmol/L for the group receiving ATOZET® and 4.69mmol/L for the group receiving *atorvastatin*. Mean change in calculated LDL-C from untreated baseline was 54% for ATOZET® 10/20mg; 56% for ATOZET® 10/40mg* and 61% for ATOZET® 10/80mg*.[7]

*Strengths not available in Hong Kong
[a]*p<0.01* for combination therapy vs. corresponding dose of *atorvastatin* alone

- For every 1mmol/L reduction in LDL-C, **22%** relative reduction in the incidence of any major vascular event over 5 years[1]

Study design: A randomized, double-blind, placebo-controlled, balanced-parallel group trial was conducted to test the hypothesis that the coadministration of *ezetimibe* with *atorvastatin* would result in a significantly greater reduction in LDL-C than *atorvastatin* alone. 628 patients were randomly assigned to 1 of 10 treatments: placebo, *ezetimibe* 10mg, *atorvastatin* 10mg, *ezetimibe* 10mg plus *atorvastatin* 10mg, *atorvastatin* 20mg, *ezetimibe* 10mg plus *atorvastatin* 20mg, *atorvastatin* 40mg, *ezetimibe* 10mg plus *atorvastatin* 40mg, *atorvastatin* 80mg, or *ezetimibe* 10mg plus *atorvastatin* 80mg. The primary efficacy endpoint was the percentage reduction in direct LDL-C from baseline to final assessment for the intent-to-treat population. [7]

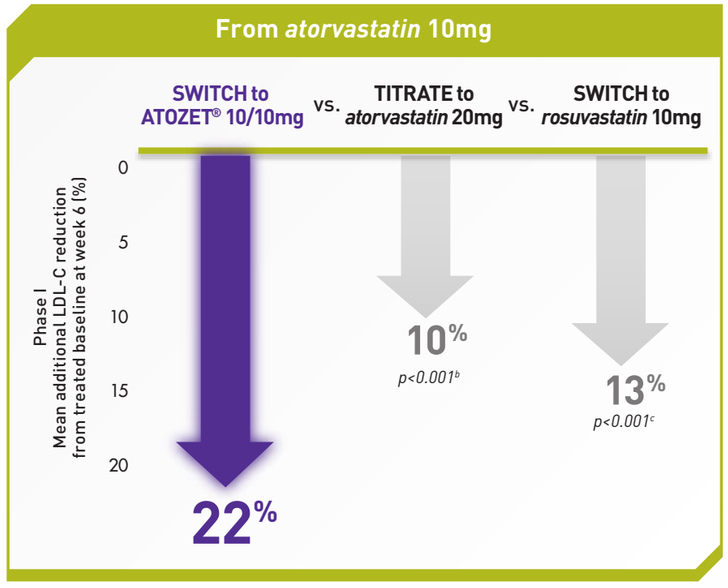
Abbreviation: LDL-C=low-density lipoprotein cholesterol

ATOZET® has been shown to be bioequivalent to coadministration of corresponding doses of *ezetimibe* and *atorvastatin* tablets.[11]

ATOZET® (*ezetimibe* and *atorvastatin*)

In a study of high-risk patients with hypercholesterolemia[a] not at LDL-C<2.6mmol/L on *atorvastatin* 10mg,

Switching to ATOZET® 10/10mg provided greater LDL-C reduction versus doubling *atorvastatin* to 20mg or switching to *rosuvastatin* 10mg[8]



The mean statin-treated baseline LDL-C was 3.13mmol/L for the group receiving **ATOZET® 10/10mg** (n=120), 3.10mmol/L for the group titrated to *atorvastatin* 20mg (n=483), and 3.13mmol/L for the group that switched to *rosuvastatin* 10mg (n=944).[8]

[a]Based on National Cholesterol Education Program Adult Treatment Panel III guidelines
[b]ATOZET® 10/10mg vs *atorvastatin* 20mg
[c]ATOZET® 10/10mg vs *rosuvastatin* 10mg

- **Significantly more patients reached LDL-C<1.8mmol/L** after 6 weeks by switching to **ATOZET® 10/10mg (19%)** vs. titrating to *atorvastatin* 20mg (3%) and switching to *rosuvastatin* 10mg (7%) (*p<0.001* for both comparison)[8]

Study design: The PACE study was a randomized, double-blind, active-controlled, multicenter study of 1,547 patients aged 18 to <80 years with primary hypercholesterolemia and high CV risk who had LDL-C≥2.6mmol/L and ≤4.14mmol/L while on *atorvastatin* 10mg. The study was split into 2 phases, each 6 weeks. Patients in phase I received *ezetimibe* 10mg add-on to *atorvastatin* 10mg vs. doubling *atorvastatin* to 20mg or switching to *rosuvastatin* 10mg. Phase II patients did not achieve an LDL-C target of <2.6mmol/L after phase I, and received either the addition of *ezetimibe* 10mg to *atorvastatin* 20mg or doubled the *atorvastatin* dose from 20mg to 40mg, or switched from *rosuvastatin* 10mg to *ezetimibe* 10mg plus *atorvastatin* 20mg or doubled *rosuvastatin* to 20mg. Primary efficacy was the percent change from treated baseline LDL-C levels at the end of phase I. Secondary efficacy comparisons included the percentages of patients achieving LDL-C<2.6mmol/L or <1.8mmol/L among the same groups[8]

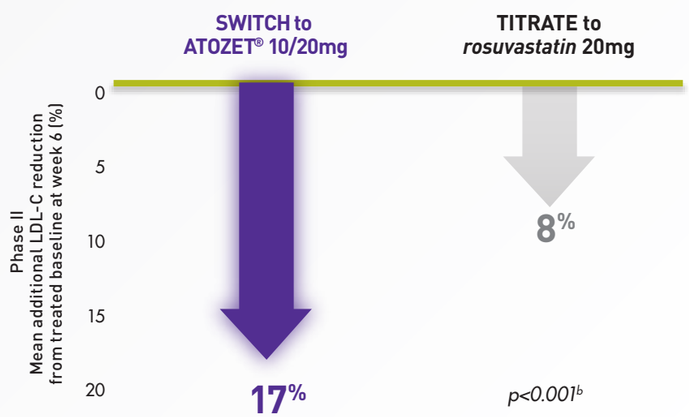
Abbreviations: CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol

ATOZET® has been shown to be bioequivalent to coadministration of corresponding doses of *ezetimibe* and *atorvastatin* tablets.[11]

In the same study of high-risk patients with hypercholesterolemia[a], among those patients still not at LDL-C<2.6mmol/L, after 6 weeks of treatment at the end of phase I

Switching to ATOZET® 10/20mg provided greater LDL-C reduction versus doubling to *rosuvastatin* 20mg or *atorvastatin* 40mg[8]

From *rosuvatation* 10mg

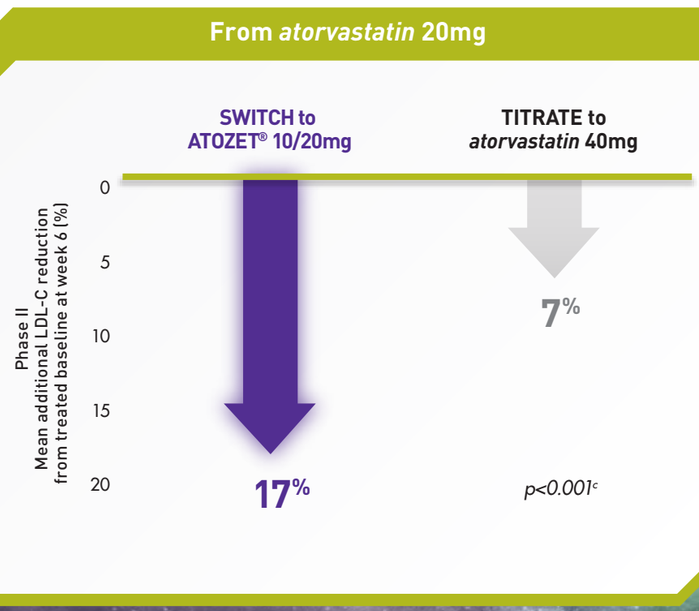


Mean baseline LDL-C for receiving **ATOZET® 10/20mg** (n=234) was 3.08mmol/L, and 3.10mmol/L for those titrated to *rosuvastatin* 20mg (n=206)[8]

Significantly more patients reached LDL-C<1.8mmol/L at week 6 after phase II by switching to **ATOZET® 10/20mg (15%)** or titrating to *rosuvastatin* 20mg (3%) *(p<0.001)*[8]

[a]Based on National Cholesterol Education Program Adult Treatment Panel III guidelines
[b]ATOZET® 10/20mg vs. *rosuvastatin* 20mg

From *atorvastatin* 20mg



Mean baseline LDL-C for receiving **ATOZET® 10/20mg** (n=124) was 3.08mmol/L, and 3.13mmol/L for those titrated to *atorvastatin* 40mg (n=126)[8]

Significantly more patients reached LDL-C<1.8mmol/L at 6 weeks after phase II by switching to **ATOZET® 10/20mg (18%)** or titrating to *atorvastatin* 40mg (1%) *(p<0.01)*[8]

[a]Based on National Cholesterol Education Program Adult Treatment Panel III guidelines
[c]ATOZET® 10/20mg vs. *atorvastatin* 40mg

Study design: The PACE study was a randomized, double-blind, active-controlled, multicenter study of 1,547 patients aged 18 to <80 years with primary hypercholesterolemia and high CV risk who had LDL-C>2.6mmol/L and ≤4.14mmol/L while on *atorvastatin* 10mg. The study was split into 2 phases, each 6 weeks. Patients in phase I received *ezetimibe* 10mg add-on to *atorvastatin* 10mg vs. doubling *atorvastatin* to 20mg or switching to *rosuvastatin* 10mg. Phase II patients did not achieve an LDL-C target of <2.6mmol/L after phase I, and received either the addition of *ezetimibe* 10mg to *atorvastatin* 20mg or doubled the *atorvastatin* dose from 20mg to 40mg, or switched from *rosuvastatin* 10mg to *ezetimibe* 10mg plus *atorvastatin* 20mg or doubled *rosuvastatin* to 20mg. Primary efficacy was the percent change from treated baseline LDL-C levels at the end of phase I. Secondary efficacy comparisons included the percentages of patients achieving LDL-C<2.6mmol/L or <1.8mmol/L among the same groups.[8]

Abbreviations: CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol

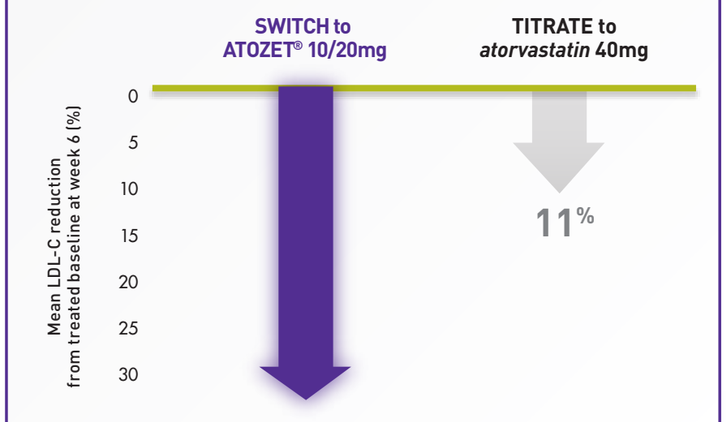
ATOZET® has been shown to be bioequivalent to coadministration of corresponding doses of *ezetimibe* and *atorvastatin* tablets.[11]

ATOZET® (*ezetimibe* and *atorvastatin*)

In a study of patients with hypercholesterolemia at moderately high-risk[a] for coronary heart disease not at LDL-C<2.6mmol/L on *atorvastatin* 40mg

Switching to ATOZET® 10/20mg provided superior LDL-C lowering efficacy versus doubling the dose of *atorvastatin*[9]

From *atorvastatin* 20mg

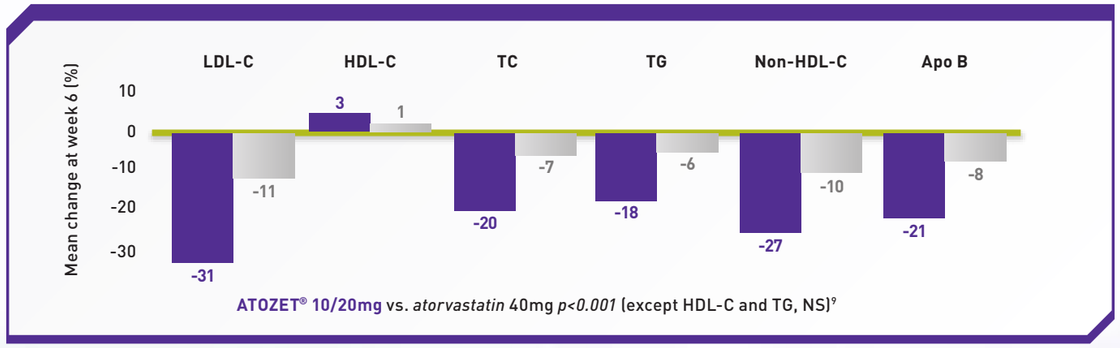


Mean baseline LDL-C for receiving **ATOZET® 10/20mg** (n=92) was 3.10mmol/L, and 3.05mmol/L for those titrated to *atorvastatin* 40mg (n=92)[9]

Significantly more patients reached LDL-C<2.6mmol/L at week 6 by switching to **ATOZET® 10/20mg (84%)** or titrating to *atorvastatin* 40mg (49%) *(p<0.001)*[9]

[a]Based on National Cholesterol Education Program Adult Treatment Panel III guidelines
[b]ATOZET® 10/20mg vs. *atorvastatin* 40mg

ATOZET® 10/20mg showed comparable changes in lipid levels to *atorvastatin* 40mg[9]



Study design: The TEMPO study was an international, multicenter, double-blind, randomized, parallel-group, titration 6-week study, including 196 patients. The study was designed to evaluate the efficacy and safety profile of ATOZET® 10/20mg compared with doubling *atorvastatin* to 40mg/day in patients with hypercholesterolemia at moderate risk of CHD who did not reach LDL-C goal<2.6mmol/L with *atorvastatin* 20mg. Patients receiving *atorvastatin* 20mg with LDL-C>2.6mmol/L and ≤4.13mmol/L were randomized to receive ATOZET® 10/20mg or *atorvastatin* 40mg. The primary end point was the mean percentage change from baseline LDL-C. Secondary end points included percentage of patients achieving LDL-C<2.6mmol/L and the percentage change from baseline to 6 weeks in TC, TG, HDL-C, non-HDL-C, apo B and high-sensitivity C-reactive protein.[9]

Abbreviations: ApoB=apolipoprotein B; CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; NS=not significant; TC=total cholesterol; TG=triglycerides

ATOZET® has been shown to be bioequivalent to coadministration of corresponding doses of *ezetimibe* and *atorvastatin* tablets.[11]

ATOZET® was generally well-tolerated in multiple clinical trials[12]

ATOZET® has been evaluated for safety in more than 2,400 patients in 7 clinical trials[11,12]

The following common (≥1/100, <1/10) or uncommon (≥1/1,000, <1/100) drug-related adverse experiences were reported in patients taking ATOZET®:

System organ class	Frequency and adverse reactions	
Infections and infestations	Uncommon:	influenza
Psychiatric disorders	Uncommon:	depression; insomnia; sleep disorder
Nervous system disorders	Uncommon:	dizziness; dysgeusia; headache; paresthesia
Cardiac disorders	Uncommon:	sinus bradycardia
Vascular disorders	Uncommon:	hot flush
Respiratory, thoracic, and mediastinal disorders	Uncommon:	dyspnea
Gastrointestinal disorders	Common:	diarrhea
	Uncommon:	abdominal discomfort; abdominal distension; abdominal pain; abdominal pain lower; abdominal pain upper; constipation; dyspepsia; flatulence; frequent bowel movements; gastritis; nausea; stomach discomfort
Skin and subcutaneous tissue disorders	Uncommon:	acne; urticaria
Musculoskeletal and connective tissue disorders	Common:	myalgia
	Uncommon:	arthralgia; back pain; muscle fatigue; muscle spasms; muscular weakness; pain in extremity
General disorders and administration site conditions	Uncommon:	asthenia; fatigue; malaise; edema
Investigations	Uncommon:	ALT and/or AST increased; alkaline phosphatase increased; blood CPK increased; gamma-glutamyltransferase increased; hepatic enzyme increased; liver function test abnormal; weight increased

In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST≥3 × ULN, consecutive) was 0.6% for patients treated with ATOZET®. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; ULN=upper limit of normal

References: 1. Mach, F. *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. doi:10.1093/eurheartj/ehz455 **2.** Garber, A. J. *et al*. Consensus Statement by the American Association of Clinical Endocrinologists and American Collage of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. *Endocrine Practice*. 25, 69-100 (2019). **3.** Grundy, S. M. *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/ NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 73, e285–e350 (2019). **4.** Gitt, A. K. *et al*. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis*. 266,158-166 (2017). **5.** Cannon, C. P. *et al*. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 372(25), 2387-2397 (2015). **6.** TIMI Study Group. IMPROVE_IT Main Study Results. Available at: www.timi.org/index.php?page=improve-it-timi-40-slide-sets. Accessed on 24 Sept 2019. **7.** Ballantyne, C. M. *et al*. Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia - A Prospective, Randomized, Double-Blind Trial. *Circulation*. 107,2409–2415 (2003). **8.** Bays, H. E. *et al*. Efficacy and Safety of Ezetimibe Added to Atorvastatin Versus Atorvastatin Uptitration or Switching to Rosuvastatin in Patients With Primary Hypercholesterolemia. *Am J Cardiol*. 112,1885–1895 (2013). **9.** Conard, S. E. *et al*. Efficacy and Safety of Ezetimibe Added on to Atorvastatin (20 mg) Versus Uptitration of Atorvastatin (to 40 mg) in Hypercholesterolemic Patients at Moderately High Risk for Coronary Heart Disease. *Am J Cardiol*. 102(11),1489-1494 (2008). **10.** Worldwide Product Circular (ezetimibe). **11.** Hong Kong Product Circular (Atozet, MSD). **12.** Data on file, MSD.