Clinical studies with Krka's atorvastatin in the management of patients with hyperlipidemia

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Key words
Cardiovascular disease, prevention, hyperlipidemia, LDL cholesterol, atorvastatin

Abstract
Hyperlipidemia is one of the most important risk factors for cardiovascular diseases and an important priority for their prevention, while LDL cholesterol (LDL-C) represents the main target for its treatment. According to the European hyperlipidemia guidelines, statins are the first-line therapy for LDL-C lowering, due to their high efficacy and well documented effects in reducing cardiovascular as well as all-cause mortality. Atorvastatin is one of the most potent and widely used statins, with numerous clinical studies establishing its clinical benefits. Clinical study results for Krka's atorvastatin Atoris are consistent with the findings of these studies and provide evidence that Atoris affects the overall lipid profile in a dose-related manner, with good safety, along with possessing pleiotropic effects, proven in different groups of patients.

Introduction

Cardiovascular diseases (CVDs) are chronic diseases developing throughout life and usually already progressing to an advanced stage by the time symptoms occur. Coronary heart disease (CHD) is the most prevalent among CVDs and is associated with high mortality and morbidity. CVDs also remain the major cause of premature death in Europe, since of all deaths in Europe before the age of 75 years, 42% are due to CVDs in women and 38% in men. The causes of CVDs are multifactorial. Smoking, lack of physical activity and dietary habits are lifestyle-related and therefore modifiable risk factors. In contrast to age and sex which are non-modifiable, also elevated blood pressure, diabetes and hyperlipidemia are modifiable risk factors. Various studies showed that, among many other risk factors contributing to the development of CVDs, hyperlipidemia, along with hypertension, plays one of the most significant roles.[1]

Hyperlipidemia, as one of the major risk factors for CVDs, is an important priority in their prevention. According to European guidelines, the main treatment target in hyperlipidemia is LDL cholesterol (LDL-C). The guidelines recommend a 'the lower the better' approach for LDL-C lowering. The target level of LDL-C in primary prevention is, according to treatment guidelines, set below 3 mmol/l. The limit is set even lower in secondary prevention, where it is below 2.5 mmol/l or even 1.8 mmol/l, if feasible. According to the European hyperlipidemia guidelines, statins are the first-line therapy for LDL-C lowering, due to their high efficacy and well documented effects in reducing cardiovascular and all-cause mortality. On the other hand, other lipid-lowering medicines have failed to improve clinical outcomes in patients with and without CVD. Furthermore, statins have also been shown to slow the progression or even promote the regression of coronary atherosclerosis.[1–3]

A possible way of achieving the low target lipid levels recommended in the guidelines is the use of high-potency statins, such as atorvastatin. Atorvastatin reduces cardiovascular morbidity and

mortality by lowering the blood cholesterol levels in primary as well as in secondary prevention of CVDs, along with exerting additional non-lipid effects, the so-called pleiotropic effects.[4]

The lipid-lowering effects of atorvastatin and Atoris

Atorvastatin is one of the most potent and widely used statins in the world.[5, 6] It shares the mechanism of action with other statins. It is a selective and reversible competitive inhibitor of HMG-CoA reductase with a potent lipid-lowering effect that is comparable to that of rosuvastatin and more potent than that of older statins.[5] Over 400 randomised clinical studies, involving more than 80,000 patients, have been conducted to evaluate the efficacy and safety of atorvastatin in different groups of patients.[6, 7]
Atorvastatin affects the overall lipid profile in a dose-related manner. Up-titration from a 10 mg to an 80 mg daily dose of atorvastatin results in a reduction of LDL-C levels from 36% to 53%. It also significantly reduces the total cholesterol (TC) and triglyceride (TG) levels and increases the HDL cholesterol (HDL-C) levels. It consequently enables more patients to reach their target lipid levels compared to older statins. Additionally, a greater reduction in lipid levels means a greater reduction of the risk for cardiovascular events.[5]
Findings from other atorvastatin clinical studies are, in terms of efficacy, consistent with those reported in the following clinical studies conducted with Krka's atorvastatin Atoris: ATOP, ATLANTICA, FARVATER, OSCAR and INTER-ARS, which have demonstrated that Atoris is effective in a wide range of patients in both primary and secondary prevention of CVDs. The studies have confirmed the effects of Atoris on the overall lipid profile, its LDL-C lowering effect in a linear dose-related manner and clear advantages of dose up-titration on the reduction of LDL-C. In addition, the INTER-ARS study has indicated a similar efficacy of Atoris and the original atorvastatin in decreasing LDL-C, TC and TG.[8–12]
The efficacy results of Krka's studies with Atoris are presented in Table 1.

Higher doses for a stronger effect on lipid levels

The guidelines for the management of hyperlipidemia as well as the guidelines for CVD prevention have placed greater emphasis on reaching target lipid levels and introduced lower target lipid levels for patients at very high risk. In these patients, LDL-C should be lowered to below 1.8 mmol/l or, if this is unachievable, by at least 50%.[1, 2] A meta-analysis has shown that every 1.0 mmol/l reduction in LDL-C is associated with a corresponding 20–25% reduction in CVD mortality and non-fatal myocardial infarction.[13] Further analyses have also shown that reduction of the major cardiovascular events is directly proportional to the absolute LDL-C reduction and that further benefit is gained from more intensive statin therapy even if LDL-C is already lower than 2.0 mmol/l.[14] Moreover, other clinical studies have indicated that even a small reduction of LDL-C has a significant clinical effect, since every 1% reduction in the LDL-C reduces the relative risk for major CHD events by approximately 1%. Therefore, every 1% reduction counts and leads to a greater clinical benefit for the patient.[15]
However, in everyday clinical practice statins are usually prescribed at the lowest dose possible and often not up-titrated to achieve the therapeutic goals. Not up-titrating the dose of statin is one of the main reasons why over half of all coronary patients, and four out of five of all high-risk patients, are not achieving the lipid goals and, as a consequence, are not achieving the maximum benefits of the preventive strategies. The challenge for the clinical practice is therefore to initiate appropriate treatment in both patients with established CVD and patients at high risk of developing CVD by up-titrating the dose of the statin to attain the lipid goals.[1]
The advantages of up-titrating atorvastatin were demonstrated in the ATLANTICA study, Krka's clinical study with Atoris. This multicentre study included 655 patients of an average age of 60 years. Over 90% of the patients were eligible for secondary prevention and over 80% of them had CHD that was mostly manifested as angina pectoris and in 25% of the patients as myocardial infarction in the past; 85% of the patients had arterial hypertension and 10% had diabetes mellitus. The aim of this study was to compare the efficacy and safety of atorvastatin therapy in patients treated with Atoris 10 mg with those receiving Atoris 10 to 80 mg (the mean dose at the end of the study

was 28.6 mg) and those receiving conventional treatment, which also included hypolipidemic agents (control group). The most significant reduction of LDL-C by 38.6%, TC by 29.7%, TG by 15.7% and elevation of HDL-C by 15.7% after 24 weeks were observed in patients that were receiving more intensive atorvastatin therapy compared to patients that were treated either with Atoris 10 mg or with conventional treatment. The target levels (primary prevention patients ≤ 3 mmol/l; secondary prevention patients ≤ 2.5 mmol/l) of LDL-C were also achieved in more patients in the group with increased dosage of Atoris, compared to the group treated with low doses of Atoris. Thus, the ATLANTICA study has confirmed the proven benefits of Atoris up-titration and proved that increasing the dose of atorvastatin enables more patients to reach target lipid levels and, as a consequence, enables the maximum benefits of LDL-C reduction.[8]

The efficacy of atorvastatin and Atoris in different types of patients

Atorvastatin has undergone extensive clinical evaluation which proved it suitable for the treatment of patients with various lipid disorders and additional comorbidities. It was extensively evaluated in controlled clinical studies that included patients with acute coronary syndrome (MIRACLE, PROVE-IT TIMI-22), type 2 diabetes mellitus (CARDS) and arterial hypertension (ASCOT-LLA), patients with CHD and patients after myocardial infarction (TNT, IDEAL). Atorvastatin was also evaluated in studies investigating the regression of coronary atherosclerosis (REVERSAL).[4, 16–21] The above described groups of patients are regularly included in Krka's clinical studies with Atoris. For instance, the ATOP study was designed to establish the efficacy and safety of Atoris in high-risk patients, patients with metabolic syndrome, patients with CHD, patients with occlusive disease of non-coronary arteries and in patients with diabetes. Three hundred and thirty-four patients were treated with 10–40 mg of Atoris for a period of 12 weeks. The initial dose (10 mg or 20 mg) was up-titrated if after the first 6 weeks of the treatment the target levels of LDL-C were not achieved. At the end of the study the mean daily dose of Atoris was 21.3 mg. An analysis of the efficacy of Atoris showed significant reductions of TC by 26%, LDL-C by 36% and TG by 9% (Table 1). Its effect on lipid levels was similar in all analysed groups of patients (Figure 1).[9]

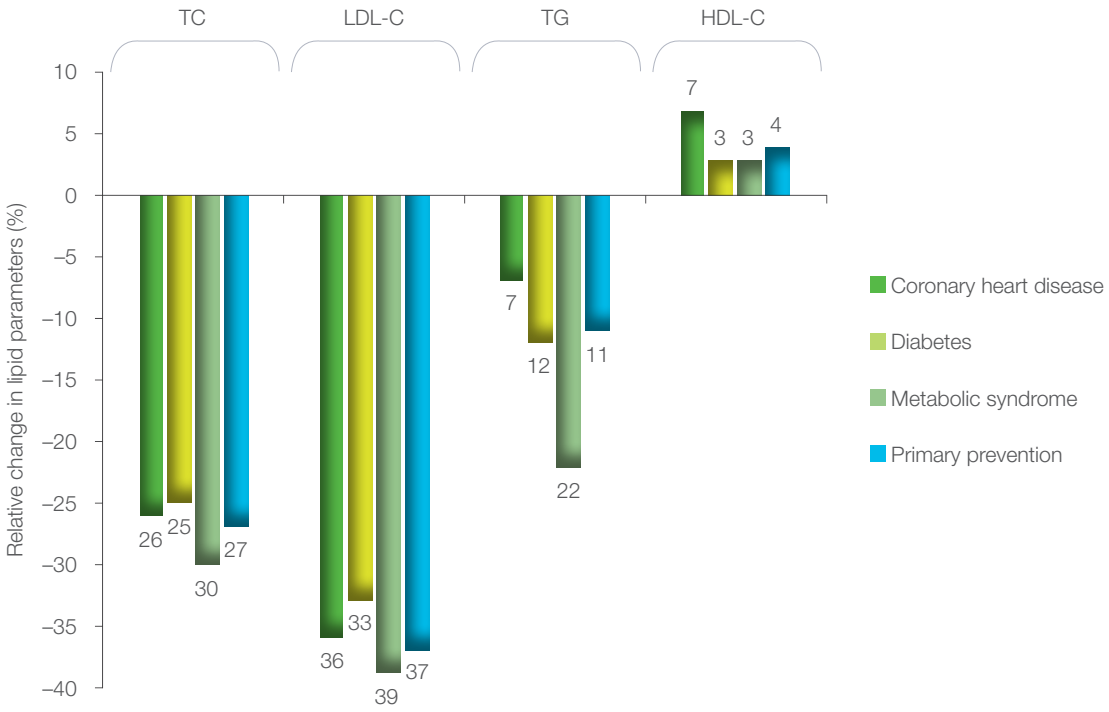

Figure 1. Relative change in lipid parameters in different groups of patients in the ATOP study[9]

The target LDL-C level (primary prevention patients ≤ 3 mmol/l; secondary prevention patients ≤ 2.5 mmol/l) was attained in 50.3% of the patients. The highest percentage of patients (68.2%)

who reached the target LDL-C level had metabolic syndrome. Similar results were noticed in the group of patients in primary prevention (65.3%). In contrast, a smaller percentage of patients achieved the target LDL-C levels in the remaining two groups: in the group of patients with diabetes 45.9% and in the group with CHD 43.4%.[9] These results are comparable with the results from the REALITY study, which took place in 10 European countries and included 58,223 patients. Its results showed that 40.5% of patients on average reached the target LDL-C and/or TC levels.[22] Finally, Krka's prospective study ATOP confirmed the therapeutic efficacy and safety of Atoris in a large number of patients in both primary and secondary prevention.[9]

Another Krka's study evaluated the effects of Atoris on lipid metabolism, microcirculation and daily ECG monitoring parameters in patients with acute coronary syndrome (ACS). This open comparative study included 98 ACS patients with or without ST segment elevation and hyperlipidemia. The patients were randomly assigned to two comparable groups and were treated with nitrates, antiaggregants, anticoagulants, fibrinolytics, β-blockers and angiotensin converting enzyme (ACE) inhibitors. Patients in one group were also given Atoris 40 mg once daily for a period of 30 ± 4 days in addition to standard therapy. Atoris was administered on day 1 or day 2 of ACS. All patients in the Atoris group attained the target levels of TC (≤ 5.2 mmol/l) and LDL-C (≤ 2.5 mmol/l) after 1 month of therapy, with significant reductions of TC by 43.5%, LDL-C by 54.4% and TG by 26.0%. Moreover, after 30 days of treatment, effort angina improved by one or more functional classes in 53.6% of the patients in the Atoris group and in 42.1% of the patients in the control group. A significant improvement was also observed in the level of endothelial activity: the microcirculation index increased by 11.6% in patients receiving conventional therapy, while the most significant increase was observed in patients receiving atorvastatin by 29.4%. The parameters of daily ECG monitoring demonstrated a reduction of 23.8% ($p < 0.05$) in the duration as well as overall incidence of ischemic events in the Atoris group. The positive effect of atorvastatin on the parameters of daily ECG monitoring is probably associated with the favourable dynamics of platelet aggregation, improvement of blood flow properties, normalisation of lipid metabolism and, consequently, with the regression of endothelial dysfunction. This improves the prognosis of the disease, increases the survival rate and indicates the benefits of Atoris in the treatment of patients with ACS.[23]

Reaching the treatment target and beyond

In recent years a number of clinical studies have provided evidence about positive pleiotropic effects of statins that, in addition to their hypolipidemic activity, play an important role in the improvement of the endothelial function, decrease of inflammatory activity and remodelling of the vascular wall. Indeed, statins quickly normalise endothelial function, inhibit platelet aggregation and thrombus formation, reduce vascular inflammation and prevent rupture of atherosclerotic plaques, thus improving microcirculation. Stabilisation of rupture-sensitive atherosclerotic plaques can prevent the development of serious complications of the CHD. It was also established that the decrease of the number of cardiovascular events during long-lasting therapy with statins is largely attributable to pleiotropic effects of these medicines (Figure 2).[24–27]

These pleiotropic effects were also evaluated in one of Krka's clinical studies with Atoris, the FARVATER study. Fifty patients with CHD and primary hyperlipidemia were randomised into two groups, which were treated with a stable dose of atorvastatin (10 or 20 mg/day) for 24 weeks in order to evaluate the effects of atorvastatin on lipid levels, endothelial function, vascular wall distensibility and stiffness. LDL-C levels were reduced by 34.9% and 43.9%, respectively ($p < 0.001$). In the study period atorvastatin therapy also increased endothelium-dependent vasodilatation by 40–51% and common carotid artery distensibility by 43–45%, and reduced vascular wall stiffness by 23–26%. An improvement in the indexes showing the condition of the vascular wall was observed only after 6 months of treatment. Hence, it can be assumed that in patients with non-familial hyperlipidemia positive vascular effects of atorvastatin therapy can be expected earlier than in one year of the beginning of the therapy. Furthermore, under the influence of hypolipidemic therapy, the vascular wall becomes more distensible and less stiff.[11]

A subgroup analysis of the pleiotropic effects was also performed in 148 patients in the ATLANTICA study. These patients were included in a non-invasive ultrasound testing of endothelium-dependent vasodilatation of brachial artery, since the goal was to assess the endothelium function as one of the parameters of the pleiotropic effects of statins. During this study the number of patients with pronounced endothelium dysfunction statistically significantly decreased by 26% in the group of patients on higher doses of Atoris. This effect was observed already after 12 weeks of treatment, while decreases were not statistically significant in the other two groups treated either with a low dose of Atoris or receiving conventional treatment. The results of the ATLANTICA study clearly demonstrated the advantages of atorvastatin up-titration over low-dose and conventional treatment with regard to the effects on lipid parameters as well as pleiotropic effects, which were observed in a reduced number of patients with pronounced endothelial dysfunction.[8]

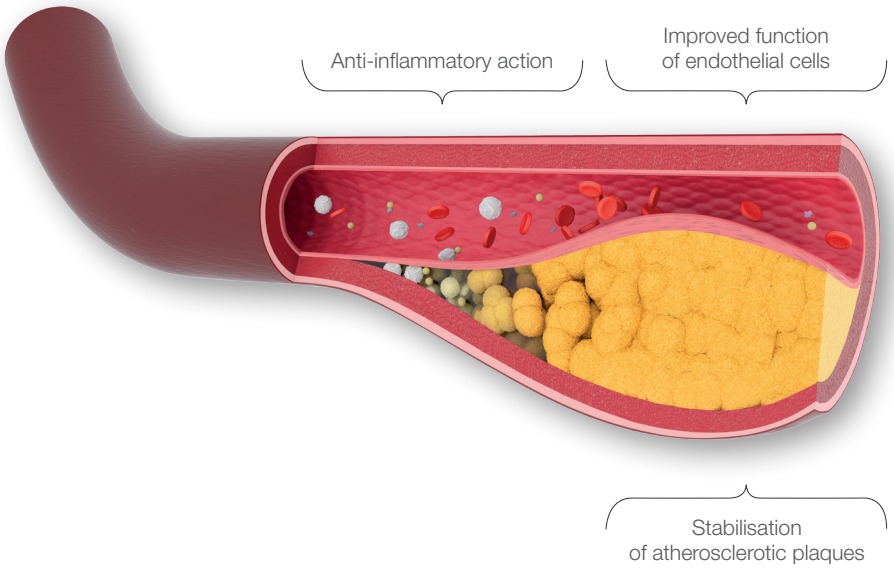

Figure 2. Pleiotropic effect of statins

The safety profiles of atorvastatin and Atoris

Extensive data from randomised clinical studies, post marketing analyses as well as reports to regulatory agencies demonstrated the safety of atorvastatin in a large number of patients with a variety of indications. A retrospective analysis of 44 completed studies, including 16,495 hyperlipidemia patients, treated with atorvastatin, placebo or other statins, revealed that only 3% of atorvastatin-treated patients withdrew from studies due to adverse reactions, compared to 1% of those receiving placebo and 4% of those receiving other statins. The most frequently reported adverse reactions were related to the digestive system, while serious adverse reactions were rare and seldom led to withdrawal. Persistent elevations in hepatic transaminases, aspartate transaminase or alanine transaminase, to more than 3 times the upper limit of normal were experienced in only 0.5% of atorvastatin-treated patients. A persistent elevation in creatine kinase was observed in only one atorvastatin-treated patient and was not associated with myopathy. The incidence of treatment-associated myalgia was low in atorvastatin (1.9%), placebo (0.8%) and other statin (2.0%) groups, and was not dose-related. No cases of rhabdomyolysis or myopathy were reported. Finally, the overall incidence of adverse reactions observed with atorvastatin was not increased in the 10–80 mg dose range and was similar to that observed in patients treated with placebo and in patients treated with other statins.[28] Other clinical studies and meta-analyses have come to similar conclusions as well, confirming the positive safety profile of atorvastatin at the highest recommended dose in a wide range of patients.[29]

The safety results from Krka's clinical studies with Atoris are consistent with the results of the safety analyses in atorvastatin clinical studies. Overall, patients tolerated Atoris therapy very

well, since adverse reactions related to the atorvastatin therapy were observed only in a few percentages of patients. Furthermore, the prospective ATOP study confirmed the safety of Atoris in a wide range of patients in both primary and secondary prevention of CVDs. Additionally, the ATLANTICA study demonstrated that the frequency of significant adverse reactions was 1.8% in the group of patients treated with 10 mg/day of atorvastatin and 0.5% in the group of patients treated with an increasing dose of atorvastatin. No significant differences were evident between the frequency of adverse reactions in the control group (conventional treatment) and that in the atorvastatin dose titration group in any phase of the study. The data from this study confirmed the good safety profile across the whole range of Atoris therapeutic dosages (10–80 mg/day). Finally, the INTER-ARS study, which compared the safety parameters of Atoris with those of the originator's atorvastatin, established comparable safety profiles between the medicines. No differences in any of the safety parameters between the study groups were found. [8–12]
The results of the safety analysis of Krka's studies with Atoris are presented in Table 1.

Conclusions

Krka is dedicated to continuously evaluating the efficacy and safety of its products. Krka's atorvastatin is the leading statin in a large part of Europe* and has been trusted by many doctors and patients for more than ten years.[30] In this period, Krka has performed a number of interventional and non-interventional post-authorisation clinical studies with Atoris, which included more than 25,000 patients.[31] The most important clinical studies, INTER-ARS, FARVATER, OSCAR, ATOP and ATLANTICA, have all confirmed the efficacy and safety of Atoris in a wide range of patients, in both primary and secondary prevention of CVDs. Thus, the above clinical studies with Atoris provide useful evidence of the benefit of atorvastatin treatment and represent an important contribution to a better management of hyperlipidemia in different groups of patients as well as the foundation of trust in Krka's products.

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Study	Primary objective	Patient profiles	No. of patients	Duration	Dose	Study results		Main conclusion
						Efficacy	Safety and tolerability	
INTER-ARS[12]	To evaluate the hypolipidemic action of Krka's ATV compared to the originator's ATV as the reference agent	High coronary risk patients with hyperlipidemia: • 40–65 years old • absolute coronary risk > 9.5% in 10 years • without diagnosed CVD	117	16 weeks	Initial dose: 10 mg/d or 20 mg/d After 6 weeks of treatment, the dose was doubled if the patient did not achieve the target LDL-C level.	LDL-C: • Krka's ATV: –37.8% • Originator's ATV: –38.4% No significant difference between treatment groups in LDL-C reduction was found. TC: • Krka's ATV: –30.3% • Originator's ATV: –29.2%	The safety of the study medicines was comparable. No increase of CK level > 10 times ULN was observed. No treatment discontinuations due to adverse reactions	Fully comparable efficacy and safety of Krka's ATV and the originator's ATV
FARVATER[11]	To evaluate the effects of Krka's ATV on lipids, C-reactive protein, fibrinogen levels and vascular wall structure and function	Patients with CHD and primary hyperlipidemia, 35–70 years old	50	24 weeks	One group received 10 mg/d and the other 20 mg/d	LDL-C: • 10 mg/d: –34.9% • 20 mg/d: –43.9% TC: • 10 mg/d: –25.4% • 20 mg/d: –27.0% Endothelium-dependent vasodilatation: • 10 mg/d: +40.2% • 20 mg/d: +51.3% Common carotid artery distensibility: • 10 mg/d: +45.3% • 20 mg/d: +43.7% Vascular wall stiffness: • 10 mg/d: –23.3% • 20 mg/d: –25.7%	The treatment with ATV was well tolerated. No cases of AST or ALT activity elevation above > 3 times ULN and CK > 10 times ULN 2 adverse reactions (allergic reaction, elevation of CK activity) linked to ATV therapy were registered.	Krka's ATV is effective and well tolerated with proven pleiotropic effects.
OSCAR[10]	To identify high-risk patients and establish the efficacy of Krka's ATV and SIM in real-life clinical practice settings	Patients with established CVD or at high CV risk, 35–75 years old	7098	8 weeks	10 mg/d of ATV or 20 mg/d of SIM	LDL-C: • Krka's ATV: –26.7% • Krka's SIM: –25,0% TC: • Krka's ATV: –22.7% • Krka's SIM: –22.7% Reduction of total CV risk by 33%	The treatment was well tolerated; adverse reactions were documented in 2.7% of the patients.	Krka's ATV and SIM have been proven to be effective and safe in real-life clinical practice settings.

Table 1. Key outcome studies with Krka's atorvastatin (Atoris)

ATV – atorvastatin, SIM – simvastatin, CV – cardiovascular, ULN – upper limit of normal, AST – aspartate transaminase, ALT – alanine transaminase, CK – creatine kinaze

Study	Primary objective	Patient profiles	No. of patients	Duration	Dose	Study results		Main conclusion
						Efficacy	Safety and tolerability	
ATOP[9]	To establish the efficacy and safety of Krka's ATV in a wide population of patients	Patients with primary hypercholesterolemia and combined hyperlipidemia (+18 years): • at high CV risk and without established CVD • metabolic syndrome • CHD • occlusive disease of non-coronary arteries and • diabetes mellitus	334	12 weeks	Initial dose: 10 mg/d or 20 mg/d After 6 weeks of treatment, the dose was doubled if the patient did not achieve the target cholesterol level.	LDL-C: –36% TC: –26% Among different groups of patients Krka's ATV had a similar effect on lipid parameters.	The treatment with ATV was well tolerated. No cases of ALT activity elevation > 3 times ULN and CK > 10 ULN were reported. 1 case of AST activity elevation > 3 times ULN was reported. 3.3% of the patients discontinued the treatment due to adverse reactions.	Krka's ATV has been proven to be effective and safe in a wide population of patients.
ATLANTICA[8]	To demonstrate the efficacy and safety of Krka's ATV in long-term treatment	Patients with hyperlipidemia, 18–75 years, with established CHD or with: • diagnosed atherosclerosis of the arteries • abdominal aortic aneurysm • type 2 diabetes mellitus • metabolic syndrome • transient ischemic attack • high CV risk	655	24 weeks	Group A: 10 mg/d Group B: 10–80 mg/d (the mean dose at the end of the study was 28.6 mg) Group C: conventional treatment	LDL-C: • Group A: –31.1% • Group B: –38.6% • Group C: –24.8% TC: • Group A: –23.1% • Group B: –28,6% • Group C: –18.2%	The treatment with ATV was well tolerated. No significant difference in the frequency of adverse events between groups in any phase of the study The frequency of significant adverse reactions was 1.8% in group A and 0.5% in group B.	The study confirmed the effect of Krka's ATV on LDL-C and its dose dependency.
ACS[23]	To investigate the role of Krka's ATV in the treatment of patients with ACS	ACS patients with hyperlipidemia, 52–70 years old, with or without ST segment elevation	98	4 weeks	40 mg/d	LDL-C: –54.4% TC: –43.5% Lowering of the functional class of effort angina (by 1 or more) in 53.6% of the patients 29.4% increase of the microcirculation index Reduction of overall incidence of ischemic events by 23.8%	The treatment with ATV was well tolerated. Clinically significant adverse reactions were not reported.	Krka's ATV at a dose of 40 mg/day is an effective medicine for the prevention of severe ischemic outcomes (CV death, stroke, myocardial infarction) and the progression of heart failure.

Table 1. Key outcome studies with Krka's atorvastatin (Atoris)

ATV – atorvastatin, SIM – simvastatin, CV – cardiovascular, ULN – upper limit of normal, AST – aspartate transaminase, ALT – alanine transaminase, CK – creatine kinaze

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Krka's medicines are marketed in different countries under different brand names.

Some products may not be available in all countries due to still valid patent protection.

For complete information on the products please refer to the Summary of Product Characteristics. You can obtain it from Krka's medical representatives.