

Krkini lijekovi – generacije znanja za bolje zdravlje bolesnika

Krka's Medicines – Generations of Knowledge for Better Health of Patients

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SAŽETAK: Vjerujte u moć znanja. U pouzdanost pri odabiru liječenja. U odanost misiji koja na prvo mjesto stavlja zdravlje. To su vrijednosti koje povezuju Krku već 70 godina. Naša je glavna svrha biti pouzdan globalni partner u zdravlju za liječnike, ljekarnike i bolesnike, dok je istodobno naša misija razvijati visokokvalitetne, sigurne i učinkovite lijekove. Nedavno je dokazano koliko je važan vertikalno integriran model proizvodnje. Taj model omogućuje nam potpun nadzor nad cijelim procesom proizvodnje, od djelatne tvari do gotovog proizvoda, čime se osigurava visoka kvaliteta. Naše inovacije dokazuju našu predanost dobrobiti potrošača. Posljednjih smo godina plasirali na tržište nekoliko vrijednih fiksnih kombinacija lijekova u jednoj tableti. One uključuju kombinacije antihipertenziva koje su u širokoj uporabi, kao i druge kombinacije s kojima smo bili predvodnici među farmaceutskim proizvođačima. Naš opširan portfelj lijekova nudi pomoć za najčešće bolesti te zdravstvenim djelatnicima pruža razne opcije liječenja. Također smo jedna od malobrojnih generičkih farmaceutskih tvrtki čiji su lijekovi potkrijepljeni brojnim kliničkim ispitivanjima provedenima nakon njihove registracije, a koja dokazuju njihovu učinkovitost i sigurnost u kliničkoj praksi. Već 70 godina predani smo zdravlju sadašnjih i budućih naraštaja.

SUMMARY: Trust in the power of knowledge. Reliability in choosing treatment. Loyalty to a mission that prioritizes health above all. These are the values that have been the foundation of Krka for 70 years. Our main purpose is to be a reliable global partner in health for doctors, pharmacists, and patients, while pursuing our mission to develop high-quality, safe, and effective medicines. The importance of the vertically integrated production model has been recently demonstrated. This model allows us to have complete oversight of the entire production process, from the active ingredient to the finished product, ensuring high-quality. Our innovations demonstrate our dedication to the well-being of consumers. In recent years, we have launched several valuable single-pill combinations. These include widely used combinations of antihypertensives, as well as other combinations for which we were pioneers among pharmaceutical producers. Our extensive portfolio of medicines addresses most common diseases, providing healthcare professionals with a variety of treatment options. We are also one of the few generic pharmaceutical companies whose medicines are supported by numerous post-registration clinical studies, demonstrating their effectiveness and safety in clinical practice. For 70 years, we have been committed to the health of current and future generations.

KLJUČNE RIJEČI: visokokvalitetni lijekovi, vertikalno integrirana proizvodnja, klinička ispitivanja.

KEYWORDS: high-quality medicines, vertically integrated production, clinical studies.

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Uvod

Vjerujte u moć znanja. U pouzdanost pri odabiru liječenja. U odanost misiji koja na prvo mjesto stavlja zdravlje. To su vrijednosti koje povezuju Krku već 70 godina. Već sedam desetljeća predani smo zdravlju. Uvijek nastojimo u obzir uzeti potrebe ljudi.

Introduction

Trust in the power of knowledge. Reliability in choosing treatment. Loyalty to a mission that prioritizes health above all. These are the values that have been the foundation Krka for 70 years. For seven decades now, we have been commit-

Prisutnost diljem svijeta

Naša je misija potaknuti ljude da žive zdrav život. Glavna nam je svrha biti pouzdan globalni partner u zdravlju za liječnike, ljekarnike i bolesnike. Naši lijekovi, koji potječu iz naše matične tvrtke u Sloveniji, postali su prisutni širom svijeta. Imamo proizvodna postrojenja u raznim dijelovima Europe, a sva ona održavaju iste standarde kvalitete. Naši medicinski predstavnici dijele informacije o našim lijekovima te najnovije smjernice za liječenje sa zdravstvenim djelatnicima na više od 40 tržišta diljem svijeta te ih tako podržavaju u rješavanju medicinskih problema. Danas se našim proizvodima liječi više od 100 milijuna ljudi u više od 70 zemalja. Najvažnija skupina proizvoda među njima farmaceutski su proizvodi koji se izdaju na recept.¹

Vrlo raznolika ponuda lijekova protiv najčešćih bolesti

Kardiovaskularne bolesti (KVB) već su desetljećima vodeći uzrok mortaliteta i važan čimbenik koji pridonosi onesposobljenosti. Godine 2021. čak 20,5 milijuna ljudi umrlo je od kardiovaskularne (KV) bolesti, a taj je broj činio oko trećine umrlih diljem svijeta.² Dodatno se trudimo kako bismo istražili načine optimalnoga zbrinjavanja čimbenika rizika za KVB i da bismo poboljšali medicinske intervencije za smanjenje kliničkog opterećenja povezanog s razvojem spomenutih bolesti. Povišen arterijski tlak (AT) i visoke razine lipida u krvi dva su od najčešćih KV čimbenika rizika koji se pojavljuju istodobno jer su često prisutni u iste osobe.³ To se moglo jasno vidjeti u nedavno dobivenim rezultatima epidemiološkog istraživanja *DISCOVERY*, u kojem je 54 % bolesnika imalo obje bolesti. Istraživanje je bilo prospektivno te je ispitivalo liječenje arterijske hipertenzije i/ili hiperkolesterolemije u kliničkoj praksi između 2021. i 2022. godine u skupini zemalja jugoistočne Europe s visokim ili vrlo visokim rizikom.^{4,5} Bolesnici su opažani tijekom razdoblja od 12 tjedana, a podatci su bilježeni u dvama navratima. Prikupljeni podatci odražavaju trenutačnu situaciju oko praćenja smjernica za liječenje obiju bolesti u uobičajenoj kliničkoj praksi. Sveukupno, od svih bolesnika s hipertenzijom i hiperkolesterolemijom, u samo 4,7 % oboljelih postignute su ciljne razine AT-a i LDL kolesterola definirane u smjernicama (**slika 1**).^{4,6,7}

Pomno pratimo najčešće bolesti i nudimo širok portfelj lijekova za njih. Ponosni smo što omogućujemo 1000 proizvoda za najčešće bolesti našeg vremena. Svaki dan nudimo razna rješenja osobama s hipertenzijom. Inhibitori angiotenzin-konvertaze (ACE inhibitori) i sartani dvije su od najvažnijih skupina antihipertenziva u našem trenutačnom portfelju. Od ACE inhibitora nudimo najopsežniji raspon proizvoda temeljenih na perindoprilu u Europi, od monoterapije do cijelog raspona dvojnih ili trojnih fiksni kombinacija lijekova u jednoj tableti, kao i fiksne kombinacije sa statinima. Usto, nudimo i brojne proizvode temeljene na sartanima, uključujući valsartan, losartan i telmisartan. Portfelj proizvoda sa sartanima uključuje fiksne kombinacije lijekova u jednoj tableti bazirane na sartanima koje sadrže diuretik i blokator kalcijevih kanala.¹ Za osobe s povećanim rizikom od KVB-a naš se portfelj sastoji od dvaju statina visokog intenziteta, atorvastatina i rosuvastatina, čiji je cilj smanjiti razinu LDL kolesterola za najmanje 50 %. Također nudimo fiksnu kombinaciju rosuvastatina i ezetimiba (Co-Roswera®).¹ Osim ovih lijekova, Krka

ted to health. We consistently endeavor to consider people's needs.

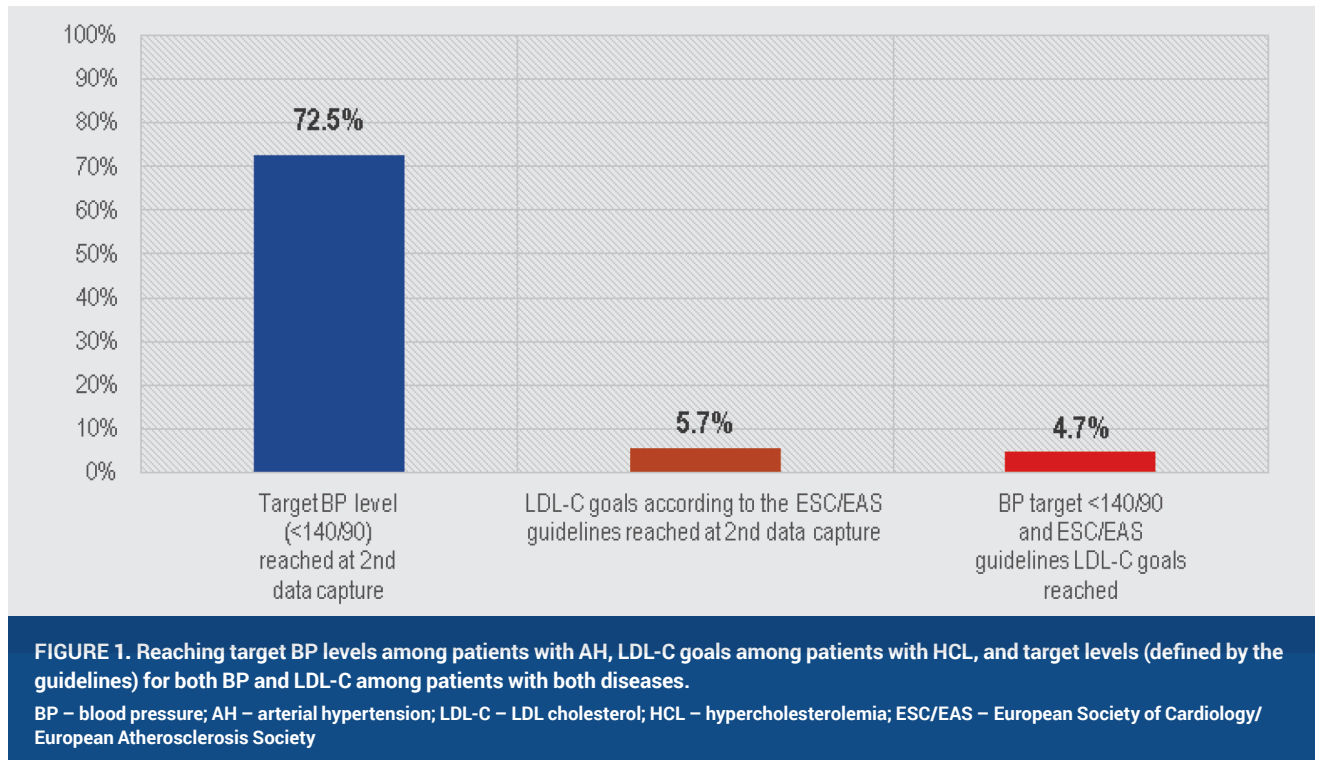
Worldwide presence

Our mission is to enable people to live a healthy life. Our main purpose is to be a reliable global partner in health for doctors, pharmacists and patients. Our medicines, originating from our parent company in Slovenia, have reached far and wide. We have established manufacturing facilities in various parts of Europe, all maintaining the same quality standards. Our medical representatives share information about our medicines and the latest treatment guidelines with healthcare professionals in over 40 markets worldwide, supporting them in solving medical issues. Today, more than 100 million people in over 70 countries are being treated with our products. Among these, the most important product group are prescription pharmaceuticals.¹

Wide variety of medicines against most common diseases

For decades, cardiovascular diseases (CVDs) have been the leading cause of mortality and a major contributor to disability. In 2021, 20.5 million people died from a cardiovascular (CV) condition, a figure that accounted for around one-third of all global deaths.² Efforts are being made to investigate ways to optimally manage risk factors for CVD and to improve medical interventions reducing the clinical burden associated with the development of the disease. High blood pressure (BP) and high levels of blood lipids are two of the most commonly co-occurring CV risk factors, as they are often present in the same individuals.³ This was evident in the recently published results of the *DISCOVERY* epidemiological study, where 54% of patients had both diseases. This was prospective study investigating the management of arterial hypertension (AH) and/or hypercholesterolemia (HCL) in real-world clinical practice between 2021 and 2022 in a cluster of South-Eastern European countries with high or very-high risk.^{4,5} Patients were observed over the course of 12 weeks, with data recorded at two time points. The collected data reflect the current situation regarding adherence to guidelines in the management of both diseases in regular clinical practice. Overall, among all patients with AH and HCL, only 4.7% reached the target BP level and LDL-cholesterol (LDL-C) goals as defined by guidelines (**Figure 1**).^{4,6,7}

At Krka, we closely monitor most common diseases and offer a wide portfolio of medicines to address them. We take pride in providing 1,000 products for most common diseases of our time. Every day, we offer a variety of solutions for individuals with hypertension. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and sartans are two of the most important classes of antihypertensives in our current portfolio. Regarding ACE inhibitors, we provide the most comprehensive perindopril-based product range in Europe, from monotherapy to a range of double or triple single-pill combinations (SPC) and SPCs with statins. Additionally, we offer many sartan-based products, including valsartan, losartan, and telmisartan. The sartan product portfolio includes sartan-based SPCs with a diuretic and a calcium channel blocker.¹ For individuals at increased CVD risk, our portfolio consists of two high-intensity statins, atorvastatin and ro-



ulazi na novo terapijsko područje antikoagulantnih lijekova s lijekom Xerdoxo® (rivaroksaban), jednim od najnaprednijih antikoagulanasa, i lijekom Daxanlo® (dabigatran).¹ Usto, pružamo opcije za glikemijsku kontrolu za širok spektar bolesnika s dijabetesom s lijekom Maysiglu® (sitagliptin, inhibitor dipeptidil peptidaze-4) ili njegovom fiksnom kombinacijom Maymetsi® (sitagliptin/metformin).¹

Visoka kvaliteta osigurava pouzdane lijekove

Naša je misija razvijati visokokvalitetne, sigurne i učinkovite lijekove te u tom pogledu ne pristajati na kompromise. Predani smo kontinuiranom ulaganju u razvoj i istraživanje te suvremenoj tehnologiji, opremi i procesima. Inovaciji, koju uključujemo u sve svoje operacije. Brojni laboratorijski testovi i analize osiguravaju sveobuhvatnu kontrolu kvalitete. Naši kvalificirani i predani timovi odani su svom radu i svojim krajnjim klijentima, bolesnicima.

Nedavno je dokazano koliko je važan naš vertikalno integriran model proizvodnje jer omogućuje tvrtki potpun nadzor nad cijelim procesom proizvodnje, od djelatne tvari do gotovoga proizvoda. Rezultat je toga visoka kvaliteta bez iznenađenja. U Europi je nekoliko proizvođača lijekova koji su sadržavali valsartan, losartan i irbesartan moralo povući svoje proizvode s tržišta zbog nitrozaminskih nečistoća. Nakon temeljite analize Europska agencija za lijekove postavila je ograničenja najviših dopuštenih razina nitrozaminskih nečistoća u proizvodima koji sadržavaju sartane sa svrhom da u budućnosti postigne nemjerljivu razinu nečistoća.⁸ Godine 2021. pojavile su se informacije o potencijalno mutagenim azidnim nečistoćama u određenim proizvodima koji sadrža-

stavastatin, aiming for at least a 50% reduction in LDL-C. We also offer an SPC containing rosuvastatin and ezetimibe (Co-Roswera®).¹ In addition to these medicines, Krka is entering a new therapeutic area with anticoagulant medicines with Xerdoxo® (rivaroxaban), one of the most advanced anticoagulants, and Daxanlo® (dabigatran).¹ Furthermore, we provide options for glycemic control for a broad spectrum of diabetic patients with Maysiglu® (sitagliptin, a dipeptidyl peptidase-4 inhibitor) or its SPC Maymetsi® (sitagliptin/metformin).¹

High-quality-assured reliable medicines

Our mission is to develop high-quality, safe, and effective medicines and to make no compromises in this regard. We are committed to continuous investments in development and research and committed to state-of-the-art technology, equipment, and processes. We are also committed to innovation, which we incorporate into all our operations. Numerous laboratory tests and analyses ensure comprehensive quality control. Our skilled and dedicated teams are devoted to their work, and their final clients, the patients.

Recently, it has been demonstrated how important our vertically integrated production model is, as it allows the company to have complete oversight of the entire production process, from the active ingredient to the finished product. This results in high quality with no surprises. In Europe, several producers of medicines containing valsartan, losartan, and irbesartan had to withdraw their products from the market due to nitrosamine impurities. After an in-depth analysis, the European Medicines Agency set limits on maximum levels of nitrosamine impurity levels in sartan-containing products with the goal of achieving no quantifiable impurities in the future.⁸ In 2021, information emerged about potentially mutagenic

vaju sartane. Posljedično je Europska direkcija za kvalitetu lijekova (EDQM) zahtijevala od proizvođača da opozovu svoje proizvode s tržišta i poduzmu odgovarajuće radnje kako bi osigurali da je razina azidnih nečistoća ispod propisanog praga.^{9,10} Ove mjere nisu utjecale na naše lijekove s valsartanom jer su znanstveno ispitane metode sinteze djelatnih tvari iz skupine sartana spriječile nastanak nitrozaminskih nečistoća. Zbog odsutnosti bilo kakvih mjerljivih razina nitrozaminskih i azidnih nečistoća (koje su otkrivene samo u tragovima, znatno ispod dopuštenog praga), naši su valsartani ostali dostupni bolesnicima bez ograničenja još od svojeg plasiranja na tržište.^{11,12} Za nekoliko Krkinih lijekova, uključujući i naš valsartan, EDQM je izdao certifikat o prikladnosti, koji čini najviši standard kvalitete u Europi.^{11,13,14}

Nagrađene inovacije dokazuju našu predanost dobrobiti potrošača. Naši stručnjaci neprestano traže nova rješenja koja će olakšati liječenje i poboljšati pridržavanje s terapijom, što potom dovodi do boljih terapijskih ishoda. Posljednjih je godina Krka na tržište plasirala nekoliko vrijednih fiksni kombinacija lijekova u jednoj tableti, uključujući vrlo često primjenjivane kombinacije ACE inhibitora ili sartana s diureticima ili amlodipinom, kao i trojne kombinacije s objema tvarima. Također nudimo kombinacije statina i ezetimiba, koje su ključne za pružanje intenzivnih oralnih terapija za smanjenje razina lipida brojnim bolesnicima s povećanim KV rizikom. Naš portfelj uključuje kombinacije s kojima smo bili predvodnici među farmaceutskim proizvođačima, kao što je kombinacija rosuvastatin/perindopril/indapamid (Roxiper[®]) za istodobno liječenje hipertenzije i hiperkolesterolemije, koja je dostupna u Hrvatskoj.

Osim toga što su povećali naše mogućnosti proizvodnje, optimirani procesi proizvodnje također su poboljšali i kvalitetu djelatnih tvari te smanjili opasan otpad. To smanjuje naš negativan utjecaj na okoliš te osigurava održivu budućnost. Preko dijaloga sa stručnjacima, neprestano tražimo rješenja imajući na umu ljude i okoliš. Taj uloženi trud rezultirao je našom prvom ESG ocjenom održivosti 2023. godine, koja nas je pozicionirala među 10 % najboljih farmaceutskih tvrtki u svijetu.¹

Dokazivanje kliničke djelotvornosti

Naši su lijekovi klinički dokazani – podržavamo vas u vašemu samouvjerenom pristupu kliničkoj praksi. Krka je jedna od malobrojnih generičkih farmaceutskih tvrtki čiji su lijekovi potkrijepljeni velikim brojem kliničkih ispitivanja provedenima nakon njihova registriranja. Nakon što se lijek plasira na tržište njegova djelotvornost i sigurnost prate se u svakodnevnoj praksi putem kliničkih ispitivanja koja omogućuju šire znanje i bolju upoznatost s lijekovima tvrtke. S našim je lijekovima provedeno nekoliko međunarodnih intervencijskih kliničkih ispitivanja, uključujući *INTER-ARS* (Atoris[®])¹⁵, *HEMERA* (Ampril[®] i Lorista[®] i njihove fiksne kombinacije)¹⁶, *ROSU-PATH* (Roswera[®])¹⁷, *VICTORY* (Valsacor[®] i njegove fiksne kombinacije)¹⁸ i *PRECIOUS* (Dalneva[®] i Co-Dalneva[®])^{19,20} Ta klinička ispitivanja pridonose znanstvenim postignućima, znanstveno su opravdana te se provode u skladu s primjenjivim zakonskim propisima, smjernicama o dobroj praksi i etičkim standardima. Stoga su podatci dobiveni spomenutim kliničkim ispitivanjima vjerodostojni i točni. Usto, s našim su lijekovima provedena i brojna neintervencijska klinička ispitivanja, u kojima su bolesnici praćeni u uobičajenoj kliničkoj

azido impurities in certain sartan-containing products. As a result, the European Directorate for the Quality of Medicines (EDQM) required producers to recall their products and take appropriate actions to ensure that the level of azido impurities was below the threshold levels.^{9,10} Our valsartan medicines were not affected by these measures because the scientifically evaluated synthesis routes of the sartan active ingredients prevented the formation of nitrosamine impurities. Due to the absence of any quantifiable levels of nitrosamine and azido impurities (which were detected only in traces, significantly below the permissible limit), our valsartans have remained available to patients without restriction since their launch.^{11,12} Several of Krka's medicines, including our valsartan, have obtained a Certificate of Suitability issued by the EDQM, which represents the highest quality standard in Europe.^{11,13,14}

Award-winning innovations demonstrate our dedication to the well-being of consumers. Our experts continuously seek new solutions to make treatment easier and improve adherence, which in turn enhances therapeutic outcomes. In recent years, Krka has launched several valuable SPCs, including widely used combinations of ACE inhibitors or sartans with diuretics or amlodipine, as well as triple combinations with both. We also offer combinations of statins and ezetimibe, which are crucial for providing intensive oral lipid-lowering therapies to many patients at increased CV risk. Our portfolio includes combinations for which we were pioneers among pharmaceutical producers, such as the rosuvastatin/perindopril/indapamide combination (Roxiper[®]) for the concomitant treatment of AH and HCL available in Croatia.

Optimized production processes have not only increased our production capacity but also improved the quality of active substances and reduced hazardous waste. This reduces our negative impact on the environment and ensures a sustainable future. In dialogue with experts, we continually seek solutions with people and the environment in mind. These efforts resulted in our first ESG sustainability rating in 2023, positioning us among the top 10% of pharmaceutical companies worldwide.¹

Demonstrating clinical efficacy

The effectiveness and efficacy of our medicines are clinically proven – we support you in your confident approach to clinical practice. Krka is one of the few generic pharmaceutical companies whose medicines are supported by a large number of post-registration clinical studies. After a medicine is launched on the market, its efficacy and safety are monitored in everyday practice through clinical studies, providing more in-depth knowledge and familiarity with the company's medicines. Several international interventional clinical studies have been conducted with our medicines, including *INTER-ARS* (Atoris[®])¹⁵, *HEMERA* (Ampril[®] and Lorista[®] and their single-pill combinations)¹⁶, *ROSU-PATH* (Roswera[®])¹⁷, *VICTORY* (Valsacor[®] and its single-pill combinations)¹⁸ and *PRECIOUS* (Dalneva[®] and Co-Dalneva[®])^{19,20} These clinical trials contribute to scientific achievements, are scientifically justified, and are conducted in compliance with applicable legal requirements, good practice guidelines, and ethical standards. Therefore, the data obtained from these clinical trials are credible and accurate. Additionally, numerous non-interventional clinical studies, monitoring patients in regular clinical practice and following established treatments, have been

praksi i koja su pratila dobro uhodane terapije. Najnovije ispitivanje koje je u tijeku jest istraživanje *DIVERSITY*, u kojem se ispituju Krkin sitagliptin i njegova fiksna kombinacija s metforminom u raznim skupinama bolesnika s dijabetesom tipa 2. Privremena analiza istraživanja *DIVERSITY* pokazala je statistički značajno smanjenje razina hemoglobina A1c, glukoze u plazmi natašte i postprandijalne glukoze nakon šest mjeseci liječenja. Oba su lijeka, u pravilu, bila dobro podnošljiva, bez znatnog rizika od hipoglikemije. Nadalje, unatoč tomu što je većina bolesnika s komorbiditetima imala hipertenziju, dodavanje sitagliptina ili fiksne kombinacije sitagliptin/metformin nije povećalo rizik od KV komplikacija.

Djelotvornost i sigurnost naših lijekova dokazane su u velikom rasponu bolesnika, u više od 150 kliničkih ispitivanja, koja su uključivala gotovo 350 000 bolesnika iz 27 zemalja.¹ Stoga su rezultati tih kliničkih ispitivanja jedna od ključnih dodanih vrijednosti Krkinih lijekova te pridonose točnim i pouzdanim odlukama u svakodnevnoj skrbi za bolesnike.

Zaključak

Već 70 godina predani smo zdravlju sadašnjih i budućih naraštaja. U povodu te godišnjice naša je najveća želja ostati vaš pouzdan partner. Nastavit ćemo raditi zajedno s vama kako bismo ispunili zajedničku misiju: **živjeti zdrav život**.

conducted with our medicines. The latest ongoing study is the *DIVERSITY* study on Krka's sitagliptin and its SPC with metformin in various groups of type 2 diabetic patients. The interim analysis of the *DIVERSITY* study demonstrated a statistically significant reduction in hemoglobin A1c, fasting plasma glucose, and postprandial glucose after six months of treatment. Both medicines were generally well-tolerated, without a significant risk of hypoglycemia. Furthermore, despite the majority of patients with comorbidities having AH, adding sitagliptin or sitagliptin/metformin SPC did not appear to increase the risk of CV complications.

The efficacy and safety of our medicines have been demonstrated in a wide range of patients, in over 150 clinical studies, and involving nearly 350,000 patients from 27 countries.¹ Therefore, the results of these clinical studies are one of the key added values of Krka's medicines, contributing to accurate and reliable decisions in everyday patient care.

Conclusion

For 70 years, we have been committed to the health of current and future generations. On this anniversary, our greatest wish is to remain your reliable partner. We will continue to work together with you to fulfil our common mission: **living a healthy life**.

LITERATURE

- Annual report 2023. Krka, d. d., Novo mesto, 2024. [cited 2024 June 18]. Available from: <http://www.krka.biz/en/>
- Di Cesare M, Bixby H, Gaziano T, Hadeed L, Kabudula C, McGhie DV, et al. World Heart Report 2023: Confronting the World's Number One Killer. Geneva, Switzerland. World Heart Federation. 2023 [cited 2024 June 18]. Available from: <https://world-heart-federation.org/resource/world-heart-report-2023/>
- Perrone V, Veronesi C, Gambera M, Nati G, Perone F, Tagliabue PF, et al. Treatment with Free Triple Combination Therapy of Atorvastatin, Perindopril, Amlodipine in Hypertensive Patients: A Real-World Population Study in Italy. *High Blood Press Cardiovasc Prev*. 2019 Oct;26(5):399-404. <https://doi.org/10.1007/s40292-019-00336-2>
- Statistical analysis report. International real-world study exploring the management of arterial hypertension and hypercholesterolemia. Data on file. Krka d. d., Novo mesto, Slovenia. 2023
- Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2021 Sept 7;42(34):3227-337. <https://doi.org/10.1093/eurheartj/ehab484>
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J*. 2018 Sept 1;39(33): 3021-104. <https://doi.org/10.1093/eurheartj/ehy339>
- Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, 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*. 2020 Jan 1;41(1):111-88. <https://doi.org/10.1093/eurheartj/ehz455>
- Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities. European medicine agency. 2019 [cited 2024 June 18]. Available from: <https://www.ema.europa.eu/en/news/sartan-medicines-companies-review-manufacturing-processes-avoid-presence-nitrosamine-impurities>
- Risk of presence of mutagenic azido impurities in sartan active substances with a tetrazole ring. European Directorate for the Quality of Medicines & HealthCare. 2021 [cited 2024 June 18]. Available from: <https://www.edqm.eu/en/-/risk-of-presence-of-mutagenic-azido-impurities-in-sartan-active-substances-with-a-tetrazole-ring>
- Risk of the presence of mutagenic azido impurities in losartan active substance. European Directorate for the Quality of Medicines & HealthCare. 2021 [cited 2024 June 18]. Available from: <https://www.edqm.eu/en/-/risk-of-the-presence-of-mutagenic-azido-impurities-in-losartan-active-substance>
- Grošelj M, Barbič-Žagar B. Krka's Added-value Generic Medications. *Cardiol Croat*. 2019;14(5-6):146-9. <https://doi.org/10.15836/ccar2019.146>
- Krka's sartans not affected by the recalls due to azido impurities. Krka website. 2021 [cited 2024 June 18]. Available from: <https://www.krka.biz/en/media-centre/news/krkas-sartans-not-affected-by-the-recalls-due-to-azido-impurities/12514/>
- EDQM Certification. EDQM [cited 2024 June 18]. Available from: https://extranet.edqm.eu/publications/recherches_CEP.shtml
- Marinšek G, Glavač Povhe A, Milovanović Jarh D, Barbič-Žagar B. High-quality Valsartans Contributing to the Treatment of Hypertension and Beyond for More than 15 Years. *Cardiol Croat*. 2022;17(7-8):134-9. <https://doi.org/10.15836/ccar2022.134>
- Boh M, Opolski G, Poloński L, Zambrzycki J, Poredos P, Ceska R. Porównanie skuteczności i bezpieczeństwa stosowania atorwastatyny generycznej i referencyjnej u osób zwiększonego ryzyka wieńcowego z hiperlipidemią. *Kardiologia po Dypłomie*. Wydanie Specjalne. 2006;3-9.
- Chazova IE, Martyniuk TV. [Possibilities of rational combination antihypertensive therapy: results of HEMERA international clinical trial]. *Ter Arkh*. 2013;85(10):10-22. Russian. **PubMed**: <https://pubmed.ncbi.nlm.nih.gov/24437213/>

17. Cevc M, Dan GA, Karadi I, Lutai M, Reiner Z, Shiyakhto E, et al. The efficacy and safety of rosuvastatin in a wide population of patients with hyperlipidemia and the placement of additional strengths of 15 mg and 30 mg in clinical practice. The ROSU-PATH trial: international, randomized, open-label, prospective trial. *Krka website*. 2021 [cited 2024 June 18]. Available from: <https://www.krka.biz/en/for-professional-public/kmf/prescription-pharmaceuticals/cardiovascular-diseases/rosupath/>
18. Accetto R, Chazova IY, Sirenko Y, Vincelj J, Widimsky J Jr, Barbič-Žagar B. The efficacy and safety of valsartan and combination of valsartan and hydrochlorothiazide in the treatment of patients with mild to moderate arterial hypertension - the VICTORY trial. *Kardiol Pol*. 2017 Jan;75(1):55-64. <https://doi.org/10.5603/KP.a2016.0135>
19. Brguljan J, Chazova I, Gaciong Z, Simic D, Vajer P, Zelveian, et al. Effect of single pill combinations on central systolic blood pressure. *J Hypertens*. 2022 June;40(Suppl 1):p e304. <https://doi.org/10.1097/01.hjh.0000838696.92081.37>
20. Brguljan J, Chazova IE, Gaciong Z, Simic D, Vajer P, Zelveian PH, et al. Single-pill combination enables fast target BP achievement. *J Hypertens*. 2023 Jan; 41(Suppl 1):p e394-e395. <https://doi.org/10.1097/01.hjh.0000916860.25615.9f>