Slovensko Farmacevtsko Društvo
SLOVENIAN PHARMACEUTICAL SOCIETY

Sekcija bolnišničnih farmacevtov Slovenije
Section of Slovenian Hospital Pharmacists

16. mednarodni simpozij

(16th International Symposium)

USPEŠEN ZDRAVSTVENI SISTEM IN PODOBNA BIOLOŠKA ZDRAVILA: ALI OBSTAJA POVEZAVA?

HEALTH SYSTEMS CAN'T AFFORD NOT TO HAVE BIOSIMILARS: HOW TO MAKE THEM A SUCCESS?

Zbornik povzetkov in izročkov

(Book of abstracts and handouts)

Ljubljana, 5. november 2024

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Kazalo vsebine

Predstavitev predavateljev

Speaker Introductions

Arnold G. Vulto

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Ustanova / *Institution*: Erasmus University Medical Center, Dept. Of Hospital Pharmacy, Rotterdam, The Netherlands

Kratka predstavitev / *Short introduction:*

Arnold G. Vulto je mednarodno priznan strokovnjak na področju bioloških zdravil, zlasti podobnih bioloških zdravil. Preko svojega podjetja VuPEC (www.vupec.com) izobražuje in svetuje farmacevtskim podjetjem, vladam, regulativnim organom in drugim organizacijam o trgu podobnih bioloških zdravil in politiki na tem področju. Pogosto je vabljen kot govornik na konferencah in izobraževalnih dogodkih o podobnih bioloških zdravilih po vsem svetu.

Profesor Vulto je (so)avtor več kot 230 mednarodnih strokovno pregledanih člankov (povezava: https://pure.eur.nl/en/persons/arnold-vulto) ter je doslej nadzoroval skupno 50 specializantov bolnišnične farmacije in doktorskih študentov. Bil je član Upravnega odbora EAHP in predsednik Znanstvenega odbora (2004-2008). Bil je član usmerjevalnega odbora in predsednik programskega odbora Prve globalne konference o prihodnosti bolnišnične farmacije (Basel, 2008). Leta 2010 je bil prof. Vulto izvoljen za člana Ameriškega kolegija klinične farmakologije (FCP). Prejel je različne nagrade, med njimi nagrado za »vizionarsko vodstvo in usmeritev« v bolnišnični farmaciji (EAHP) in nagrado Jana Gleruma za življenjsko delo zaradi prispevka k usposabljanju bolnišničnih farmacevtov. Leta 2019 je bil izvoljen za častnega člana Združenja bolnišničnih farmacevtov na Nizozemskem. Profesor Vulto je bil 8 let glavni urednik European Journal of Hospital Pharmacy Practice (2004-2012).

Profesor Vulto je eden od soustanoviteljev iniciative za generična in podobna biološka zdravila (GaBI; 2008) ter iniciativne skupine za podobna biološka zdravila na Nizozemskem (2013). Leta 2015 je bil pobudnik in voditelj Prve nacionalne konference o podobnih bioloških zdravilih na Nizozemskem. Leta 2016 je bil eden od ustanoviteljev raziskovalnega sklada MABEL na Univerzi v Leuvenu v Belgiji.

Arnold G. Vulto is an internationally renowned expert in biological medicines, especially biosimilars. Through his company VuPEC (www.vupec.com) he educates and advises pharmaceutical companies, governments, regulatory bodies, and other organizations on the market for biosimilars and biosimilars policy. He is a frequently invited speaker at biosimilars conferences / educational events all over the world.

Professor Vulto is the (co)author of more than 230 international peer reviewed papers (link: https://pure.eur.nl/en/persons/arnold-vulto) and has been supervising in total 50 hospital pharmacy residents and PhD students. He was member of the Board of Directors of the EAHP and was Chairman of its Scientific Committee (2004-2008). He was a member of the Steering Committee and chair of the Program Committee of the First Global Conference on the Future of Hospital Pharmacy (Basel, 2008). In 2010 Prof. Vulto was elected as Fellow of the American College of Clinical

Pharmacology (FCP). He received different awards: "Visionary guidance and leadership" in hospital pharmacy (EAHP) and the Jan Glerum Lifetime Achievement Award for his contribution to the training of hospital pharmacists. In 2019 he was elected as a lifetime Honorary Member of the Dutch Society of Hospital Pharmacists. Professor Vulto was for 8 years Editor in Chief of the European Journal of Hospital Pharmacy Practice (2004-2012).

Professor Vulto is one of the co-founders of the Generics & Biosimilars Initiative (GaBI; 2008) and the Initiative Group Biosimilars The Netherlands (2013). In 2015 he initiated and chaired the First National Conference on Biosimilars in The Netherlands. In 2016 he was one of the founders of the MABEL Research Fund at Leuven University, Belgium.

Aurelio Arias

Elektronska pošta/*e-mail*:

Ustanova / *Institution*: IQVIA

Kratka predstavitev / *Short introduction:*

Aurelio ustvarja strateške vsebine, ki so aktualne in usmerjene v prihodnost ter relevantne za globalne vodstvene kadre v farmaciji, pri čemer redno objavlja članke, bloge in bele knjige. Njegovo delo je osredotočeno na trge po izteku patentne zaščite, kjer z raziskavami, ki temeljijo na dokazih, spodbuja razprave o različnih temah, pomembnih za farmacevtsko industrijo. Velja za strokovnjaka na več področjih, vključno s podobnimi biološkimi zdravili, digitalnim zdravjem in ESG (okoljsko, družbeno in korporativno upravljanje), redno sodeluje na konferencah po svetu, predstavlja na sestankih upravnih odborov ter sodeluje pri svetovalnih projektih.

Aurelio creates topical and forward-looking strategic content relevant to global pharma executives and publishes articles, blogs, and white papers on a regular basis.

Aurelio focuses on off-patent markets where he generates evidence-led insights with a view to spark high-level discourse on various topics relevant to the pharmaceutical industry. He is considered a subject matter expert in several areas including biosimilars, digital health and ESG and speaks at numerous conferences worldwide, presents at board-level meetings and engages in consulting projects.

Tomaž Bratkovič

Elektronska pošta/*e-mail*: tomaz.bratkovic@ffa.uni-lj.si

Ustanova / *Institution*: Univerza v Ljubljani, Fakulteta za farmacijo, Katedra za farmacevtsko biologijo

Kratka predstavitev / *Short introduction:*

Tomaž Bratkovič je izredni profesor na Fakulteti za farmacijo Univerze v Ljubljani ter predstojnik Katedre za farmacevtsko biologijo. Kot predavatelj sodeluje pri več učnih enotah s področij celične in molekularne biologije ter farmacevtske biotehnologije na študijskih programih, ki jih organizirata UL FFA in UL BF. Med letoma 2011 in 2016 je bil član Ekspertne skupine 6 (biološke snovi) pri Evropski farmakopeji (Evropski direktorat za kakovost zdravil, Strasbourg, Francija)

Tomaž Bratkovič is an associate professor at the Faculty of Pharmacy, University of Ljubljana, and head of the Department of Pharmaceutical Biology. As a lecturer, he contributes to several courses in the fields of cellular and molecular biology and pharmaceutical biotechnology in study programs organized by the University of Ljubljana, Faculty of Pharmacy, and the University of Ljubljana, Faculty of Biology. Between 2011 and 2016, he was a member of Expert Group 6 (biological substances) at the European Pharmacopoeia (European Directorate for the Quality of Medicines, Strasbourg, France).

Simona Borštnar

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Ustanova / *Institution*: Onkološki inštitut Ljubljana

Kratka predstavitev / *Short introduction:*

Doc. dr. Simona Borštnar je specialistka internistične onkologije in interne medicine na Onkološkem inštitutu v Ljubljani. Leta 2003 je doktorirala iz klinične onkologije. V letu 2006 se je Izobraževala na onkološkem centru MD Anderson Houston Že več kot 10 let je vodja multidisciplinarnega tima za rak dojk in predsednica Združenja za senologijo pri SZD. Je tudi predsednica komisije za oceno protokolov raziskav na Onkološkem inštitutu.

Je glavna raziskovalka v številnih kliničnih študijah raka dojke in govornica na več onkoloških konferencah doma in v tujini. Njeno bibliografijo sestavlja 500 enot: od tega več kot 40 raziskovalnih člankov.

Assoc. Prof. Dr. Simona Borštnar is a specialist in medical oncology and internal medicine at the Institute of Oncology in Ljubljana. She received her PhD in clinical oncology in 2003. In 2006, she underwent training at the MD Anderson Cancer Center in Houston. For over a decade, she has been the head of the multidisciplinary breast cancer team and the president of the Senology Association of the Slovenian Medical Association. She is also the chair of the protocol review committee at the Institute of Oncology.

She is the principal investigator in numerous clinical breast cancer studies and a speaker at various oncology conferences both domestically and internationally. Her bibliography comprises 500 units, including over 40 research articles.

David Drobne

Elektronska pošta/*e-mail*:

Ustanova / *Institution*: UKC Ljubljana, KO za gastroenterologijo

Kratka predstavitev / *Short introduction:*

Zaposlen je kot gastroeneterolog na Kliničnem oddelku za gastroenterologijo UKC Ljubljana in kot docent na Katedri za Interno medicino Medicinske fakultete v Ljubljani. Njegovo ožje subspecialno področje delovanja je kronična vnetna črevesna bolezen. Poleg kliničnega dela z bolniki s kronično vnetno črevesno boleznijo sodeluje tudi v različnih raziskovalnih projektih s tega področja. Njegove raziskave so usmerjene v farmakokinetiko bioloških zdravil. Na njegovem oddelku vodijo eno večjih evropskih kohort s kronično vnetno črevesno boleznijo, zato se tudi uspešno vključujejo v mednarodne projekte.

He is employed as a gastroenterologist at the Clinical Department of Gastroenterology, University Medical Centre Ljubljana, and as an assistant professor at the Department of Internal Medicine, Faculty of Medicine, University of Ljubljana. His subspecialty is chronic inflammatory bowel disease. In addition to clinical work with patients with chronic inflammatory bowel disease, he is also involved in various research projects in this field. His research focuses on the pharmacokinetics of biological drugs. His department leads one of the largest European cohorts with chronic inflammatory bowel disease, which allows for successful participation in international projects.

Jurij Fürst

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Ustanova / *Institution*: ZZZS, Oddelek za zdravila

Kratka predstavitev / *Short introduction:*

Po končani Medicinski fakulteti v Ljubljani 1981 je sprva delal v Psihiatrični bolnišnici Ormož in nato v Zdravilišču Rogaška. Leta 1991 je končal specializacijo iz interne medicine in delal v kardiološki ambulanti. Podiplomski študij iz klinične farmakologije na Medicinski fakulteti v Zagrebu je zaključil z magisterijem l. 2001. Od leta 1999 je zaposlen na Zavodu za zdravstveno zavarovanje Slovenije kot vodja oddelka za zdravila. Sočasno je v obdobju od 2001 – 2022 delal enkrat tedensko v diabetološki ambulanti Splošne bolnišnice Celje.

Najpomembnejša naloge oddelka za zdravila ZZZS so zagotavljanje financiranja primernega nabora zdravil in živil za posebne zdravstvene namene z razumnimi cenami in zagotavljanje drugih pravic zavarovanih oseb.

After graduating at the Faculty of Medicine in Ljubljana in 1981, he worked first at the Ormož Psychiatric Hospital and then at Zdravilišče Rogaška. In 1991 he completed his specialization in internal medicine and worked in a cardiology outpatient clinic. He completed his postgraduate studies in Clinical Pharmacology at the Faculty of Medicine in Zagreb with a Master's degree in 2001. Since 1999 he has been employed at the Health Insurance Institute of Slovenia (ZZZS) as Head of the Medicines Department. Additionally, he worked once a week in the Diabetology Outpatient Clinic of Celje General Hospital from 2001 - 2022.

The most important tasks of the Medicines Department of the Health Insurance Fund (ZZZS) are to ensure the financing of medicines and foods for special medical purposes at reasonable prices and to ensure other rights of insured persons.

Iztok Holc

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Ustanova / *Institution*: Oddelek za revmatologijo, Klinika za interno medicino, UKC Maribor

Kratka predstavitev / *Short introduction:*

Prim. doc. dr. Iztok Holc, dr. med. specialist interne medicine in revmatologije, je predstojnik Oddelka za revmatologijo Klinike za interno medicino UKC v Mariboru. Kot docent za področje interne medicine je vključen v pedagoški proces na Medicinski fakulteti in Fakulteti za zdravstvene vede Univerze v Mariboru. Ob rednem kliničnem delu se ukvarja tudi z znanstveno raziskovalnim delom. Posebno veselje mu predstavlja ultrazvok v revmatologiji.

Assoc. Prof. Dr. Iztok Holc, MD, a specialist in internal medicine and rheumatology, is the head of the Department of Rheumatology at the Clinic of Internal Medicine, University Clinical Centre Maribor. As an associate professor in the field of internal medicine, he is involved in the teaching process at the Faculty of Medicine and the Faculty of Health Sciences, University of Maribor. In addition to his regular clinical work, he is also engaged in scientific research. He is particularly interested in the use of ultrasound in rheumatology.

Boštjan Jovan

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Kratka predstavitev / *Short introduction:*

Njegova poklicna kariera se je začela leta 2003 na Onkološkem inštitutu v enoti za intenzivno terapijo, kjer je sodeloval pri posodobitvi strokovnih standardov v zdravstveni negi in napisal standard za zdravstveno nego bolnikov s torakalno drenažo. Udeležil se je tudi "fast track" obravnave bolnikov po operacijah, o čemer je leta 2007 napisal strokovni prispevek.

Leta 2008 se je pridružil Kliničnemu oddelku za hematologijo, kjer je po dveh letih prevzel vlogo pedagoške medicinske sestre. Skrbi za strokovno izobraževanje zaposlenih, mentorira novo zaposlene diplomirane medicinske sestre in nadzoruje študente ter dijake. Od leta 2013 je habilitiran strokovni sodelavec Zdravstvene fakultete v Ljubljani in somentor diplomskih nalog s področja hematologije.

V sodelovanju z Zavodom za transfuzijsko medicino je opravil tečaj preskrbe in zdravljenja s krvjo ter se udeležuje strokovnih izobraževanj v Sloveniji. Od leta 2019 je predsednik Sekcije medicinskih sester in zdravstvenih tehnikov v hematologiji, kjer organizira izobraževanja in predava. Redno se udeležuje mednarodnih izobraževanj, s čimer prenaša znanje v prakso in širi znanja po Sloveniji.

His professional career began in 2003 at the Oncology Institute in the intensive care unit, where he contributed to the updating of nursing standards and authored guidelines for nursing care of patients with thoracic drains. He also participated in the "fast track" care of post-operative patients, on which he published a professional article in 2007.

In 2008, he joined the Clinical Department of Hematology, where he took on the role of pedagogical nurse after two years. He is responsible for the professional education of staff, mentoring newly hired registered nurses, and supervising students. Since 2013, he has been an academic associate at the Faculty of Health Sciences in Ljubljana and co-supervises theses in the field of hematology.

In collaboration with the Blood Transfusion Institute, he completed a course on blood supply and treatment and participates in professional training in Slovenia. Since 2019, he has been the chair of the Nursing and Health Technicians Section in Hematology, where he organizes education and lectures. He regularly attends international training, applying knowledge in practice and expanding it throughout Slovenia.

Tomislav Laptoš

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Ustanova / *Institution*: Univerzitetni klinični center Ljubljana, Lekarna

Kratka predstavitev / *Short introduction:*

Tomislav Laptoš, magister farmacije, specialist klinične farmacije, je zaposlen v Lekarni UKC Ljubljana od leta 2006, kjer sodeluje pri pripravi zdravil iz nevarnih učinkovin. Razvija optimalne poti za zdravljenje posebnih bolnikov, zlasti pri tekočih peroralnih oblikah. V multidisciplinarnem timu obravnava predvsem transplantirane nefrološke pediatrične bolnike. Od leta 2014 razvija informacijske rešitve za elektronsko predpisovanje zdravil ter je aktiven predavatelj in mentor v lekarniški dejavnosti.

Tomislav Laptoš, Master of Pharmacy and specialist in clinical pharmacy, has been employed at the UKC Ljubljana Pharmacy since 2006, where he participates in the preparation of medications from hazardous substances. He develops optimal treatment pathways for specific patients, particularly concerning liquid oral forms. In a multidisciplinary team, he primarily addresses the needs of pediatric nephrology transplant patients. Since 2014, he has been involved in the development of an information solution for electronic prescribing of medications and is an active lecturer and mentor in pharmacy practice.

Matjaž Sever

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Ustanova / *Institution*: Univerzitetni klinični center Ljubljana

Kratka predstavitev / *Short introduction:*

Prof. dr. Matjaž Sever je uveljavljen slovenski hematolog in raziskovalec s področja hematoloških malignomov in celičnih terapij. Po diplomi iz medicine na Medicinski fakulteti v Ljubljani leta 2002 se je specializiral iz interne medicine in hematologije. Svoje znanje je nadgradil z enoletnim postdoktorskim izobraževanjem na Oddelku za levkemije, MD Anderson Cancer Center, University of Texas, Houston, ZDA pod mentorstvom dr. Srdjana Verstovška, kjer se je posvetil mieloproliferativnim novotvorbam.

V letih 2014/15 se je izobraževal in delal v transplantacijski enoti Hammersmith Hospital, Imperial College London, kjer se je usposobil za transplantacijsko delo v skladu z mednarodno akreditacijo JACIE. Po vrnitvi v Slovenijo je prevzel vodenje transplantacij in naprednih celičnih terapij na Kliničnem oddelku za hematologijo UKC Ljubljana.

Njegovo raziskovalno delo obsega širok spekter področij, od simulacij kardiovaskularnega sistema do razvoja novih celičnih terapij, kot so CAR-T celične terapije in genska terapija. Je vodja in sodelavec številnih raziskovalnih projektov ter avtor številnih znanstvenih publikacij. Celotna bibliografija je dostopna na https://bib.cobiss.net/biblioweb/biblio/si/slv/conor/38069859.

Prof. Dr. Matjaž Sever is an established Slovenian hematologist and researcher in the field of hematological malignancies and cellular therapies. After graduating in medicine from the Faculty of Medicine in Ljubljana in 2002, he specialized in internal medicine and hematology. He furthered his knowledge with a one-year postdoctoral fellowship at the Department of Leukemia, MD Anderson Cancer Center, University of Texas, Houston, USA, under the mentorship of Dr. Srdjan Verstovšek, where he focused on myeloproliferative neoplasms.

In 2014/15, he trained and worked in the transplantation unit at Hammersmith Hospital, Imperial College London, where he acquired expertise in transplantation work in accordance with the international JACIE accreditation. Upon his return to Slovenia, he took over the leadership of transplantation and advanced cellular therapies at the Department of Hematology, University Clinical Centre Ljubljana.

His research covers a wide range of areas, from cardiovascular system simulations to the development of new cellular therapies such as CAR-T cell therapies and gene therapy. He is the leader and collaborator on numerous research projects and the author of numerous scientific publications. His complete bibliography is available at https://bib.cobiss.net/biblioweb/biblio/si/slv/conor/38069859.

Povzetki in izročki predavanj

Lecture Abstracts and Handouts

Podobna biološka zdravila: kaj so in kako jih razvijajo?

Biosimilars: what are they, how are they developed?

Tomaž Bratkovič

Fakulteta za farmacijo, Univerza v Ljubljani

Povzetek

Podobna biološka zdravila (PBZ) so biološka zdravila, ki so zelo podobna drugim biološkim zdravilom, že odobrenim v EU (t. i. referenčnim zdravilom ali RZ). Manjše razlike med PBZ in RZ so neizogibne, kar je posledica kompleksnosti bioloških učinkovin in proizvodnih procesov. Vendar pa je z obsežnim primerjalnim vrednotenjem kakovosti (tj. fizikalno-kemijskih, strukturnih in bioloških lastnosti), dopolnjenim z manjšimi kliničnimi raziskavami, mogoče potrditi, da te razlike niso klinično pomembne, kar pomeni, da ni pričakovati razlik v učinkovitosti in varnosti med PBZ in RZ.

Če dokažemo visoko stopnjo podobnosti med PBZ in RZ ter primerljiv varnostni profil in učinkovitost, lahko te podatke ekstrapoliramo na vse terapevtske indikacije, za katere je že odobreno RZ. S tem se izognemo nepotrebnemu ponavljanju obsežnih kliničnih raziskav, kar občutno zniža stroške razvoja PBZ in omogoči širšemu krogu bolnikov dostop do enako kakovostnih, učinkovitih in varnih bioloških zdravil.

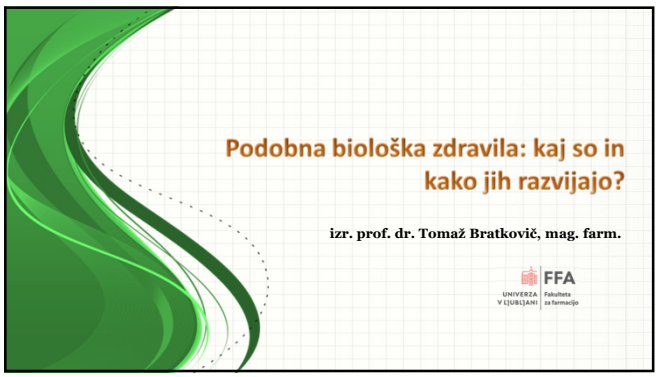
V EU imamo skoraj dvajsetletne izkušnje s PBZ. Opazovalne raziskave potrjujejo, da preklop z RZ na PBZ ali med različnimi PBZ ni povezan z varnostnimi tveganji.

Abstract

Biosimilars (BS) are biological medicines that are highly similar to other biological medicines already approved in the EU (the so-called reference medicines or RM). Minor differences between BS and RM are unavoidable due to the complexity of biological substances and manufacturing processes. However, extensive comparative assessments of quality (i.e., physicochemical, structural, and biological properties), supplemented by smaller clinical studies, can confirm that these differences are not clinically significant, meaning that no differences in efficacy and safety between BS and RM are expected.

If a high degree of similarity between BS and RM is demonstrated, along with a comparable safety profile and efficacy, this data can be extrapolated to all therapeutic indications for which the RM has already been approved. This avoids unnecessary repetition of extensive clinical studies, significantly reducing the costs of developing BS and providing broader access for patients to equally high-quality, effective, and safe biological medicines.

In the EU, we have nearly twenty years of experience with BS. Observational studies confirm that switching from RM to BS or between different BS is not associated with safety risks.


Podobna biološka zdravila: kaj so in kako jih razvijajo?
izr. prof. dr. Tomaž Bratkovič, mag. farm.
FFA
UNIVERZA V LJUBLJANI
Fakulteta za farmacijo

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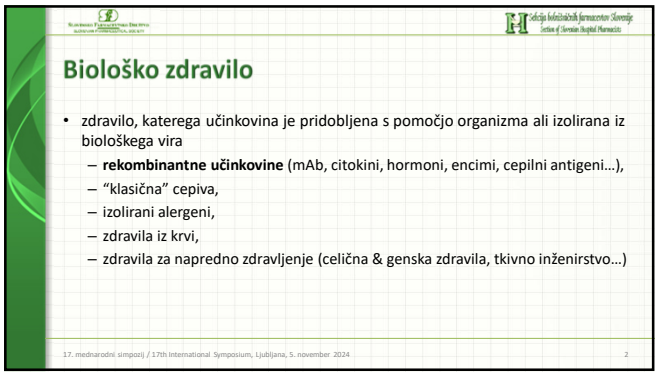
Biološko zdravilo
• zdravilo, katerega učinkovina je pridobljena s pomočjo organizma ali izolirana iz biološkega vira
– **rekombinantne učinkovine** (mAb, citokini, hormoni, encimi, cepilni antigeni…),
– "klasična" cepiva,
– izolirani alergeni,
– zdravila iz krvi,
– zdravila za napredno zdravljenje (celična & genska zdravila, tkivno inženirstvo…)
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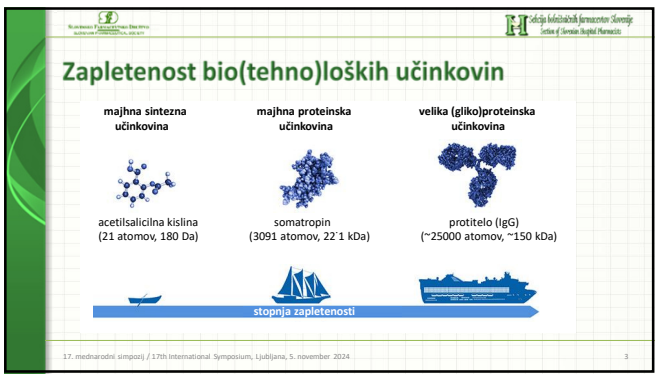
Zapletenost bio(tehno)loških učinkovin
majhna sintezna učinkovina
majhna proteinska učinkovina
velika (gliko)proteinska učinkovina
acetilsalicilna kislina (21 atomov, 180 Da)
somatropin (3091 atomov, 22´1 kDa)
protitelo (IgG) (~25000 atomov, ~150 kDa)
stopnja zapletenosti
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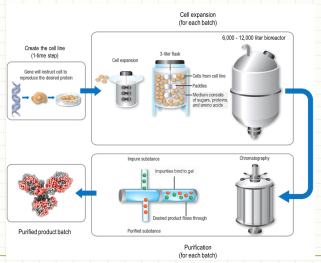
3

Proizvodnja bioloških zdravil

- proizvodni proces določa kakovost biološke učinkovine/zdravila ('The process *IS* the product!')
- zahtevana robustnost proizvodnega procesa



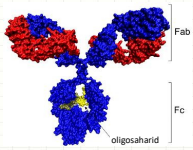
Al-Sabbagh et al., *Sem Arthritis Rheum* 2016

4

Zapletenost bio(tehno)loških učinkovin

- **strukturna zapletenost** (velikost, zvitje, disulfidne vezi, več domen/podenot, raznolikost PTM (npr. profil glikozilacije)…)
- **funkcijska zapletenost** (več mehanizmov delovanj)
- primer monoklonskih protiteles:

težka veriga
lahka veriga
glikan



določa afiniteto in selektivnost vezave antigena

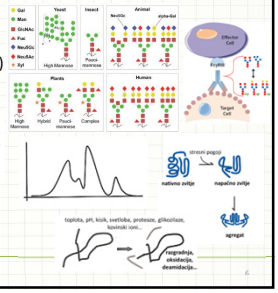
določa t.i. efektorske funkcije (mehanizmi delovanj) in $t_{1/2}$

<u>Vsi</u> deli mAb določajo učinkovitost in varnostni profil.

5

Zapletenost bio(tehno)loških učinkovin

- variabilnost bioloških učinkovin/zdravil:
  - izbor ekspresijskega sistema (celične linije)
  - bioprocesni pogoji (UPS)
  - izolacija in čiščenje (DSP)
  - formulacija
  - stabilnost
- vselej **mikroheterogenost**
- **variabilnost med serijami**
- obsežna sofisticirana analitika (komplementarne tehnike)



6

Podobno biološko zdravilo (PBZ)

- biološko zdravilo, ki je zelo **podobno drugemu, v EU že odobrenemu biološkemu zdravilu** (tako imenovanemu ***referenčnemu zdravilu*** (RZ))
- manjše **razlike** med PBZ in RZ vselej prisotne, a **niso klinično pomembne** (ni pričakovati razlik v učinkovitosti in varnosti!)
- potrebno dokazati visoko stopnjo podobnosti **strukture**, **biološke aktivnosti** in **učinkovitosti**, **varnosti** ter **profila imunogenosti**
- naslanjanje na izkušnje o učinkovitosti in varnosti, pridobljene pri referenčnem zdravilu → ponavljanje kliničnih vrednotenj nepotrebno
- obsežno **primerjalno vrednotenje** PBZ in RZ

7

PBZ niso "biogeneriki"!

LASTNOST	GENERIK	PODOBNO BIOLOŠKO ZDRAVILO
Molekulska masa učinkovine	>500-900 Da	4-150 kDa (in več)
Struktura	enostavna	zapletena, variabilnost
Način pridobivanja	sintezno – identična kopija	posebej prirejen bioproces - podobna (a nikoli identična) kopija
Zapletenost	razmeroma nizka – možno popolno ovrednotenje	prisotna heterogenost – težavno vrednotenje razlik
Zahteve	podatki o kakovosti, **bioekvivalentnost**	popoln dosje kakovosti, **dokaz podobnosti** (***comparability exercise***): kakovost, varnost, učinkovitost

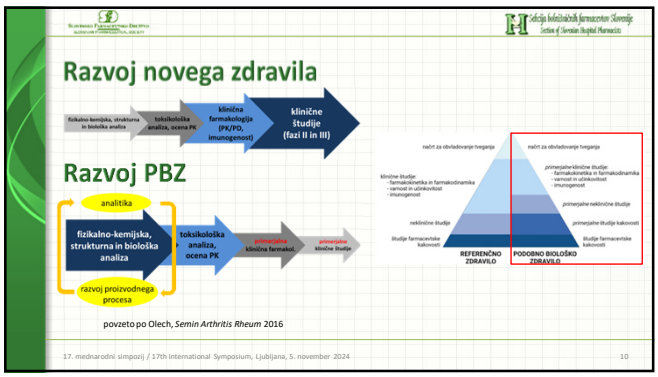
8

PBZ v EU: trenutno cca. 89 različnih

- odobritev sledi **centraliziranemu postopku** (EMA)
- EU na tem področju orala ledino (koncept PBZ uveden v legislativo že l. 2004, prvo PBZ odobreno l. 2006 (v ZDA šele l. 2015))
- splošne (kakovostne, neklinične, klinične) in produktno specifične smernice EMA (inzulini, somatropin, G-CSF, epoetini, IFNβ, FSH, mAb, nizkomolekularni heparini)
- EMA priporočila odobritev že 106 PBZ; nekatere proizvajalci umaknili iz ekonomskih razlogov

https://www.gabionline.net/biosimilars/general/biosimilars-approved-in-europe

9


Razvoj novega zdravila
fizikalno-kemijska, strukturna in biološka analiza
toksikološka analiza, ocena PK
klinična farmakologija (PK/PD, imunogenost)
klinične študije (fazi II in III)
Razvoj PBZ
analitika
fizikalno-kemijska, strukturna in biološka analiza
toksikološka analiza, ocena PK
primerjalna klinična farmakol.
primerjalne klinične študije
razvoj proizvodnega procesa
povzeto po Olech, Semin Arthritis Rheum 2016
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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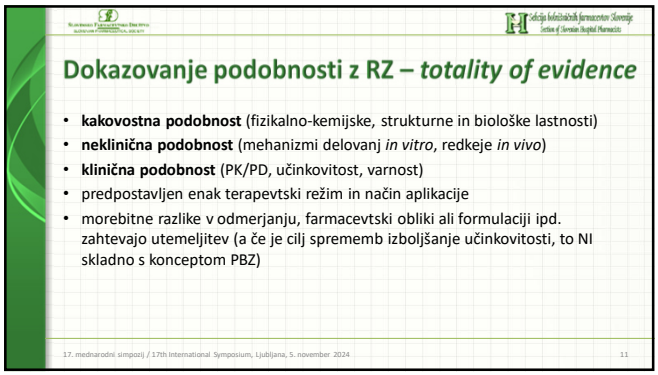
Dokazovanje podobnosti z RZ – totality of evidence
kakovostna podobnost (fizikalno-kemijske, strukturne in biološke lastnosti)
neklinična podobnost (mehanizmi delovanj in vitro, redkeje in vivo)
klinična podobnost (PK/PD, učinkovitost, varnost)
predpostavljen enak terapevtski režim in način aplikacije
morebitne razlike v odmerjanju, farmacevtski obliki ali formulaciji ipd. zahtevajo utemeljitev (a če je cilj sprememb izboljšanje učinkovitosti, to NI skladno s konceptom PBZ)
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
11

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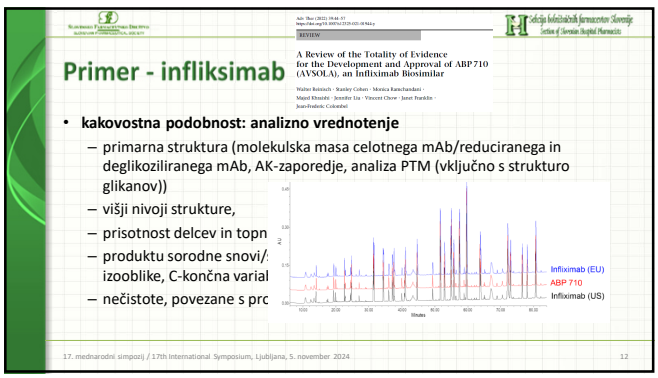
Primer - infliksimab
A Review of the Totality of Evidence for the Development and Approval of ABP 710 (AVSOLA), an Infliximab Biosimilar
kakovostna podobnost: analizno vrednotenje
primarna struktura (molekulska masa celotnega mAb/reduciranega in deglikoziliranega mAb, AK-zaporedje, analiza PTM (vključno s strukturo glikanov))
višji nivoji strukture,
prisotnost delcev in topn
produktu sorodne snovi/
izooblike, C-končna varial
nečistote, povezane s prc
Infliximab (EU)
ABP 710
Infliximab (US)
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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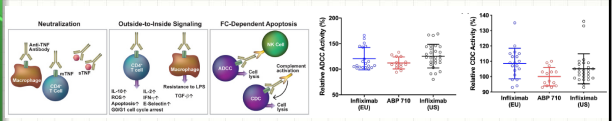
Primer - infliksimab

A Review of the Totality of Evidence for the Development and Approval of ABP 710 (AVSOLA), an Infliximab Biosimilar

- **neklinična podobnost: mehanizmi delovanj (“PD *in vitro*”)**
  - afiniteta in kinetika vezave TNF-α in FcRIIIa ter FcRn
  - celični testi (nevtralizacija TNF-α, ADCC, CDC, ADCP, neposredno proženje apoptoze…)

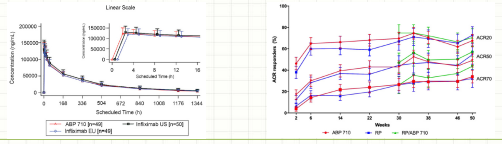


13

Primer - infliksimab

A Review of the Totality of Evidence for the Development and Approval of ABP 710 (AVSOLA), an Infliximab Biosimilar

- **klinična podobnost: PK (zdravi prostovoljci) & primerjalna klinična raziskava (bolniki z RA)**
  - bioekvivalenčna raziskava (enkratni odmerek), varnostni profil, imunogenost
  - klinična raziskava – občutljivi in objektivni izidi



14

Primer - infliksimab

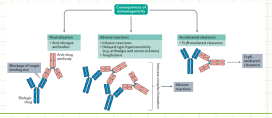
A Review of the Totality of Evidence for the Development and Approval of ABP 710 (AVSOLA), an Infliximab Biosimilar

- **klinična podobnost: primerjalna klinična raziskava (bolniki z RA)**
  - klinična raziskava – varnostni profil, imunogenost

Table 3 Safety and immunogenicity of ABP 710 and infliximab reference product (RP) in patients with rheumatoid arthritis (RA)

Safety	Through week 22		Post week 22 (after single transition)		
	ABP 710	RP	ABP 710	RP/RP	RP/ABP 710
Any AE, n (%)	144 (51.8)	158 (69.6)	150 (55.9)	69 (57.0)	89 (58.8)
Any grade ≥ 3 AE, n (%)	12 (4.3)	14 (5.0)	18 (7.5)	7 (5.8)	5 (4.2)
Any AE with outcome of death, n (%)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to infusion delay/not administered, n (%)	30 (10.8)	30 (10.8)	19 (7.9)	11 (9.1)	8 (5.7)
Infusion reactions including hypersensitivity, n (%)	22 (7.9)	37 (13.3)	20 (8.3)	12 (9.9)	7 (5.0)
Upper respiratory tract infection, n (%)	17 (6.1)	18 (6.5)	23 (9.5)	9 (7.4)	14 (11.8)
Hematological reaction, n (%)	11 (4.0)	5 (1.8)	10 (4.1)	6 (5.0)	8 (6.7)
Hypotensicity, n (%)	9 (3.2)	9 (3.2)	11 (4.6)	4 (3.3)	0 (0.0)
Serious infections, n (%)	2 (0.7)	4 (1.4)	5 (2.1)	1 (0.8)	3 (2.5)
Malignancies, n (%)	2 (0.7)	2 (0.7)	2 (0.8)	0 (0.0)	0 (0.0)

Immunogenicity	Antibody positive by week 22 with a negative or no result at baseline		Antibody positive post week 22 with a negative or no result at week 22 (after single transition)		
	ABP 710	RP	ABP 710/ABP 710	RP/RP	RP/ABP 710
Number of patients	263	264	96	45	45
Binding antibody, n (%)	149 (57.1)	160 (60.6)	29 (30.2)	19 (42.2)	18 (40.0)
Neutralizing antibody, n (%)	47 (18.0)	55 (20.8)	3 (3.1)	1 (2.2)	2 (4.4)



Strand et al., *Nat Rev Rheumatol* 2020

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Ekstrapolacija terapevtskih indikacij

- v primeru dokazane analizne podobnosti ter primerljive varnosti in učinkovitosti lahko podatke o varnosti in učinkovitosti **ekstrapoliramo na druge indikacije**, ki so že odobrene za referenčno zdravilo
- ločene klinične raziskave za vsako terapevtsko indikacijo RZ niso potrebne
- ekstrapolacija mora biti **podprta z vsemi znanstveni dokazi**, pridobljenimi v primerjalnih študijah (študije kakovosti ter klinične in neklinične študije) – zlasti PK, mehanizmi delovanj…
- infliksimab: revmatoidni artritis → ulcerozni colitis in Crohnova bolezen (odrasli & pediatrični bolniki), ankilozirajoči spondilitis, psoriatični artritis, psoriaza v plakih

16

Medsebojna zamenljivost, preklopi in lekarniško nadomeščanje PBZ

- EMA podpira medsebojno zamenljivost RZ in PBZ
- izvedba v domeni posameznih držav članic EU
- JAZMP bioloških zdravil in PBZ ne uvršča na seznam medsebojno zamenljivih zdravil, kot to velja za generična zdravila – lekarniško nadomeščanje NE
- preklop (*switching*) med odobrenimi različicami določenega biološkega zdravila z enakim pričakovanim terapevtskim učinkom je smatran kot varen; vselej poteka pod nadzorom zdravnika, bolnik mora biti obveščen

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Drug Discovery Today • Volume 24, Number 10 • October 2019

Are we ready to close the discussion on the interchangeability of biosimilars?

Hans C. Ebbers[1], hans.ebbers@biogen.com and Huub Schellekens[2], h.schellekens@uu.nl

Since the introduction of the first biosimilar the discussion about their interchangeability has persisted. The body of evidence gathered for biosimilars provides reassurance that they are approved based on a rigorous comparability exercise and do not show clinically meaningful differences to their reference products. There are no data suggesting that the risk of switching to a biosimilar in terms of increased immunogenicity is greater than switching between two batches of any biologic. The key concern around switching biosimilars is the nocebo effect, which reinforces the need for physician involvement when switching. Whereas this might argue against automatic substitution of biosimilars, it is not a biosimilars-specific concern. To increase physician confidence in biosimilars, regulators should acknowledge that biosimilars are interchangeable.

Arq Gastroenterol • 2024, v. 61 s240148

Are we ready for multiple switches between reference products and biosimilars?

Fabio Vieira TEIXEIRA[1], Laurent PEYRIN-BIROULET[2,3] and Silvio DANESE[1]

CURRENT OPINION

EXPERT OPINION ON BIOLOGICAL THERAPY

Additional Data in Expanded Patient Populations and New Indications Support the Practice of Biosimilar-to-Biosimilar Switching

Hillel P. Cohen[1] ✉ · Wolfram Bodemmueller[2]

REVIEW

Systematic review: effectiveness and safety of switching between originator infliximab and biosimilar infliximab in patients with inflammatory bowel disease

Gary R. Lichtenstein[a], Arif Soonasra[b], Mark Latymer[c], Sheena Singh[a] and Brian G. Feagan[a]

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Hvala za pozornost!
IT'S NOT JUST GOOD
KRUSTY BRAND
SEAL OF APPROVAL
IT'S GOOD ENOUGH!
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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Podobna biološka zdravila: Zakaj so dobra za nas?

Biosimilars: why are they good for us?

Arnold G. Vulto

Erasmus University Medical Center, Dept. Of Hospital Pharmacy, Rotterdam, The Netherlands

Povzetek

Podobna biološka zdravila se na trg skoraj vedno uvedejo po nižji ceni kot referenčna zdravila. S tem se na trgu ustvari konkurenca, ki vodi k nižjim cenam – ne le za podobna biološka zdravila, temveč tudi za referenčna in običajno tudi za celotno terapevtsko kategorijo zdravil. Če se to zgodi, se stroškovna učinkovitost bioloških zdravljenj izboljša. Posledično lahko pride do povečanega in zgodnejšega dostopa bolnikov do zdravljenja, odvisno od tega, kako je organiziran zdravstveni sistem. Na koncu to izboljša kakovost oskrbe in zdravje bolnikov.

V nekaterih zdravstvenih sistemih prihranki, ki jih ustvarijo podobna biološka zdravila, omogočajo prostor v proračunu za zdravila za draga nova zdravljenja. V Evropi so podobna biološka zdravila ustvarila prihranke v višini približno 10 % celotnega proračuna za zdravila, in to ob hkratnem ohranjanju enakih standardov učinkovitosti in varnosti. Za izboljšanje trajnosti zdravstvenega sistema ni boljšega načina, kot je uvajanje podobnih bioloških zdravil. V predstavitvi bo prikazanih več primerov.

Literatura:

Dutta et al. BioDrugs (2020) 34:159–170: Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price!

https://gbiomed.kuleuven.be/english/research/50000715/52577001/mabel/Keyinsights

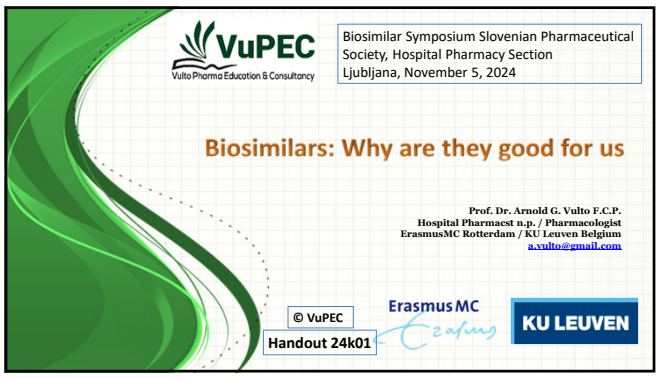
Abstract

Biosimilars are almost always introduced at a lower cost than the reference product. The resulting competition in the market leads to lower prices, not only from the biosmilar, but also for the reference product and usually also for a whole therapeutic category. If this happens, the cost-effectiviness of biological treatments is getting better. This may result in increased and earlier access of patients to treatment, depending on how the health system is organised. In the end, it will improve the quality of care and the health of patients.

In some health systems the savings induced by biosimilars gives hgeadroom in the drug bedget foor expensive new treatments. Europe wide biosimilars have generated around 10% savings on the total drug budget. And this while maintaing the same standards for efficacy and safety. There is no better way of imporving the sustainability of health care system. In the presentation several examples witll be shown.

Reference: Dutta et al. BioDrugs (2020) 34:159–170: Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price!

https://gbiomed.kuleuven.be/english/research/50000715/52577001/mabel/Keyinsights


VuPEC
Vulto Pharma Education & Consultancy
Biosimilar Symposium Slovenian Pharmaceutical Society, Hospital Pharmacy Section
Ljubljana, November 5, 2024
Biosimilars: Why are they good for us
Prof. Dr. Arnold G. Vulto F.C.P.
Hospital Pharmacst n.p. / Pharmacologist
ErasmusMC Rotterdam / KU Leuven Belgium
a.vulto@gmail.com
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Handout 24k01
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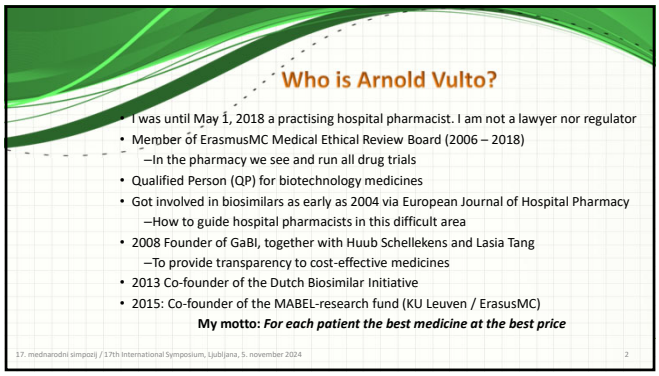
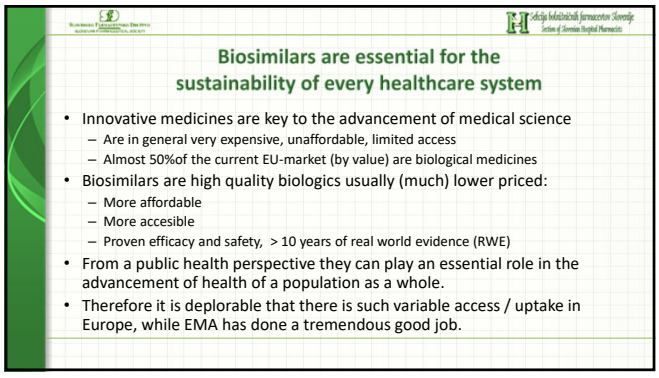
KU LEUVEN


Who is Arnold Vulto?
• I was until May 1, 2018 a practising hospital pharmacist. I am not a lawyer nor regulator
• Member of ErasmusMC Medical Ethical Review Board (2006 – 2018)
–In the pharmacy we see and run all drug trials
• Qualified Person (QP) for biotechnology medicines
• Got involved in biosimilars as early as 2004 via European Journal of Hospital Pharmacy
–How to guide hospital pharmacists in this difficult area
• 2008 Founder of GaBI, together with Huub Schellekens and Lasia Tang
–To provide transparency to cost-effective medicines
• 2013 Co-founder of the Dutch Biosimilar Initiative
• 2015: Co-founder of the MABEL-research fund (KU Leuven / ErasusMC)
My motto: For each patient the best medicine at the best price
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
2


Biosimilars are essential for the sustainability of every healthcare system
• Innovative medicines are key to the advancement of medical science
– Are in general very expensive, unaffordable, limited access
– Almost 50%of the current EU-market (by value) are biological medicines
• Biosimilars are high quality biologics usually (much) lower priced:
– More affordable
– More accesible
– Proven efficacy and safety, > 10 years of real world evidence (RWE)
• From a public health perspective they can play an essential role in the advancement of health of a population as a whole.
• Therefore it is deplorable that there is such variable access / uptake in Europe, while EMA has done a tremendous good job.

What are the gains for Europe?

- Cumulative savings (2012-2023): > 50 billion euros
- Annual savings around 10% of the TOTAL drug budget

- This is unprecedented in the history of health economics
  - No other measure ever achieved this
  - Biosimilars are the single most effective means to save money in the drug bedget

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BioDrugs
https://doi.org/10.1007/s40259-019-00395-w

REVIEW ARTICLE

Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price!

Binita Dutta[1] · Isabelle Huys[1] · Arnold G. Vulto[1,2] · Steven Simoens[1]

Competition in European off-patent biologics and biosimilar markets may expand access to the treatment, improve cost effectiveness of the treatment, increase the number of healthcare professionals, and stimulate an incremental therapeutic innovation.

1. Biosimilars induce price competition

- Due to the availability of lower cost alternatives, competition in the market is driving prices down
  - Also the cost of the innovator usually goes down (initially with a larger overall impact than just biosimilar sales)
  - We also see that the drug cost in a total therapeutic group goes down

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2. Improved cost-effectiviness

- New indications are opening up for patients, for which treatments with the innovator product was not cost-effective (and therefore not reimbursed in many countries)

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3. Expanded patient access

- As the annual treatment cost per patient decreases, more patients can be treated with biologics for the same (or sometimes: less) budget

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4. Earlier patient access

- Have you wondered why many patients got access to effective treatments in a late stage disease, missing the opportunity for cure?
- Due to lower cost of biologics, patients can be treated in an earlier stage of their disease (from 3rd line → 2nd line → 1st line)
  - This has a major positive effect on patient outcomes
- We see that treatment guidelines Europe wide are being adapted (ECCO, ESMO, EULAR etc.)

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5. Headroom for innovation

- Biosimilar savings can be re-invested in healthcare for e.g.
  - New services / additional staff
  - Improving patient care
  - Budget room for innovative new medicines

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Example: Biosimilar savings in The Netherlands (2015–2022), five molecules

Number of patients treated increased by +30%, while costs per patient decreased by an average of 70%

Molecule	Spending 2015 (M€)	Spending 2022 (M€)	Savings per molecule	Growth in no. of patients	Reduction in treatment costs per patient
Adalimumab	220.0	55.3	-75%	+86%	-87%
Etanercept	148.4	23.1	-84%	+2%	-85%
Infliximab	154.6	52.3	-66%	+50%	-77%
Rituximab	61.7	18.0	-71%	+49%	-80%
Trastuzumab	77.7	20.8	-66%	+12%	-70%
Total	**662.4**	**169.5**			

Numbers calculated from data in Dutch GIP Databank. Available at: https://www.gipdatabank.nl/.

Take home message

- The biosimilar-story is much more than just about money
  - It's about wellbeing of patients and improving treatment outcomes
- Therefore: no healthcare system can afford NOT to have biosimilars
- As hospital pharmacists we have to behave responsibly to secure the future of a healthy biosimilar market.
- I will come back to that in my later presentations today.

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Podobna biološka zdravila: Kateri so ključni dejavniki za uspeh?

Biosimilars: What are the key factors for success? The European Landscape

Aurelio Arias

IQVIA

Povzetek

V tem predavanju bomo preučili konkurenčno dinamiko na evropskem trgu z vpogledom v najnovejše trende sprejemanja pomembnih novih podobnih bioloških zdravil. Ocenjena bo konkurenca ne samo med primerljivimi podjetji, temveč tudi s strani originatorjev, kar bo zagotovilo celovit pregled konkurenčnega okolja.

Poleg tega bomo prikazali, kako se zdravniške preference glede komunikacijskih kanalov premikajo proti informacijam na zahtevo in kako se razlikujejo odnosi do preferenc bolnikov med različnimi terapevtskimi področji. Nazadnje bomo preiskali različne strategije, ki jih lahko podjetje uporabi za zagotovitev komercialnega uspeha v vse bolj prenatrpanem poslovnem okolju.

Abstract

This session will examine the competitive dynamics in the European market by taking a view at the latest uptake trends of important new biosimilar launches. Competition, not only from peer companies, will be assessed, but also from originators, providing a holistic competitive overview.

Moreover, we will show how physician preference of communication channels is shifting towards on-demand information and the differences in attitudes towards patient preference between therapy areas. Lastly, we will investigate the various strategies a company can employ to ensure commercial success in an increasingly crowded environment.

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What are the key factors for success? The European Landscape

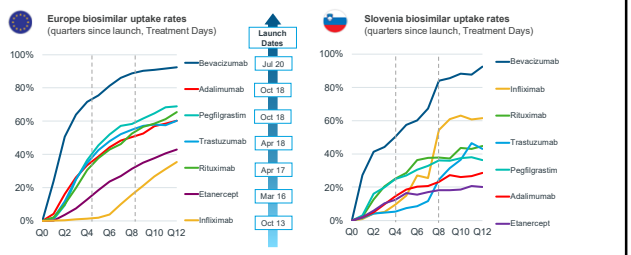
16th International Symposium; Section of Hospital Pharmacists of the Slovenian Pharmaceutical Society

Aurelio Arias
Director, EMEA Thought Leadership

0

Rate of uptake of subsequent biosimilars has accelerated as stakeholders become increasingly comfortable with biosimilars

Biosimilar market averaging 30% after Q4 and likely 50% after Q8



Notes: Includes subcutaneous formulations for rituximab, trastuzumab and infliximab
Source: IQVIA EMEA Thought Leadership; IQVIA MIDAS QTR Jun 2024

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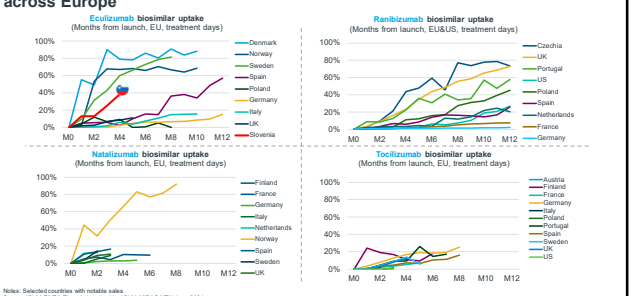
1

The introduction of new biosimilars continue to have varied adoption across Europe



Notes: Selected countries with notable sales
Source: IQVIA EMEA Thought Leadership; IQVIA MIDAS MTH June 2024
IQVIA Quarterly Pharmaceutical Market Outlook Newsletter, September 2024

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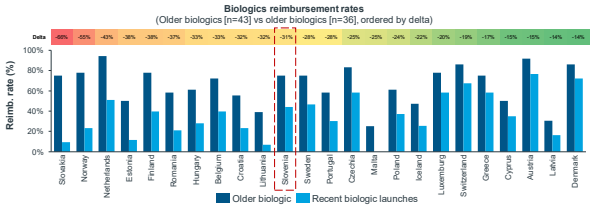
2

Access to novel innovative biologics signals longer-term challenges under the current 'innovator-linked' commercial model

The challenge is most acute in CEE countries



Is there a way to decouple the market development generated by an originator molecule, to develop a post-protection market?

Source: IQVIA WAT indicator (2022). *Novel biologic= biologics that received central marketing authorization in Europe between 2019-2021; **Older biologic= biologics that received central marketing authorization in Europe between 2014-2016

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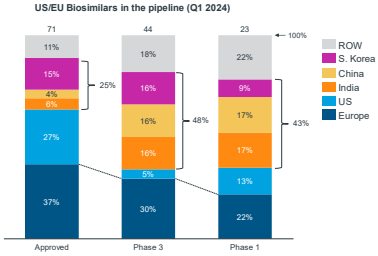
3

Supply from Asian manufacturers will increase, but their GTM strategies will differ significantly



South Korea
- Government subsidies drive competitive pricing
- Celltrion ambitious differentiated strategy
- Samsung plant 4 and 5 make it the largest CDMO in the world
  - However, now competing for manufacturing capacity

India & China
- Primarily US and regional focus, but ambitious in future scope, especially India
- Willing to operate low-cost strategies

Source: IQVIA EMEA Thought Leadership; IQVIA Institute; Data from CT.gov

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Market archetypes define critical capability requirements

Key GtM value capture drivers

BUILD THE MARKET
- Engage stakeholders
- Shape tenders
- Large f2f sales force

OPERATIONAL EXCELLENCE
- Tight management of product development
- Strong understanding of tenders
- Expand the market by driving awareness to new prescribers
- Mix of F2F and digital sales force

COMPETITIVE FOCUS
- Focus on the benefits of your brand
- RWE as potential differentiator
- Position brand to take share from market leader

NICHE AND PRICE
- Not many options aside from price
- Focus on peripheral/smaller countries
- Focus on specific indications or types of physicians
- High use of digital

Source: IQVIA EMEA Thought Leadership

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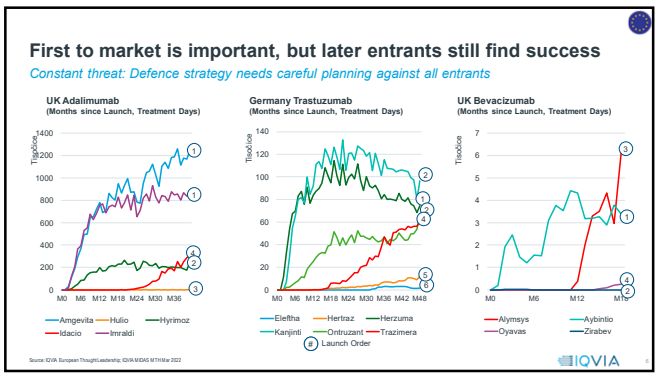
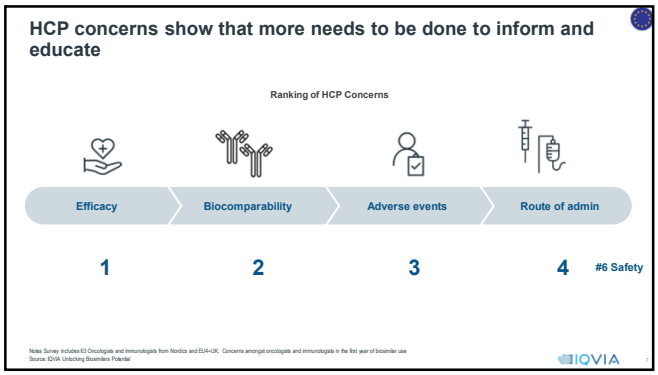
5


First to market is important, but later entrants still find success
Constant threat: Defence strategy needs careful planning against all entrants
UK Adalimumab
(Months since Launch, Treatment Days)
Germany Trastuzumab
(Months since Launch, Treatment Days)
UK Bevacizumab
(Months since Launch, Treatment Days)
Tisočice
Amgevita
Hulio
Hyrimoz
Idacio
Imraldi
Eleftha
Hertraz
Herzuma
Kanjinti
Ontruzant
Trazimera
Launch Order
Aiymsys
Aybintio
Oyavas
Zirabev
IQVIA

6


HCP concerns show that more needs to be done to inform and educate
Ranking of HCP Concerns
Efficacy
Biocomparability
Adverse events
Route of admin
1
2
3
4
#6 Safety
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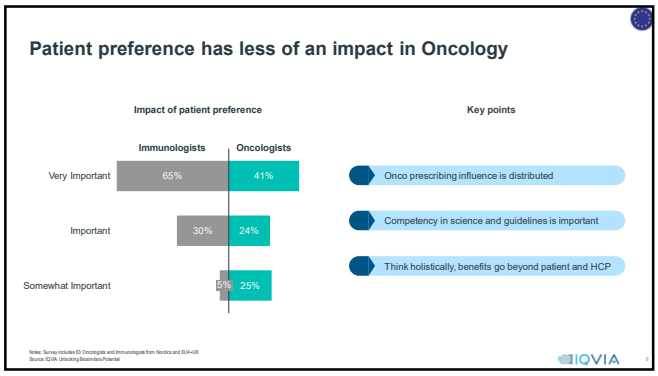
7


Patient preference has less of an impact in Oncology
Impact of patient preference
Key points
Immunologists
Oncologists
Very Important
65%
41%
Important
30%
24%
Somewhat Important
5%
25%
Onco prescribing influence is distributed
Competency in science and guidelines is important
Think holistically, benefits go beyond patient and HCP
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8

Thank you

Discover more:

Source: IQVIA EMEA ThoughtLeadership

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9

Podobna biološka zdravila: ekstrapolacija indikacij namesto kliničnih raziskav

Biosimilars: extrapolation of indications instead of clinical trial

Arnold G. Vulto

Erasmus University Medical Center, Dept. Of Hospital Pharmacy, Rotterdam, The Netherlands

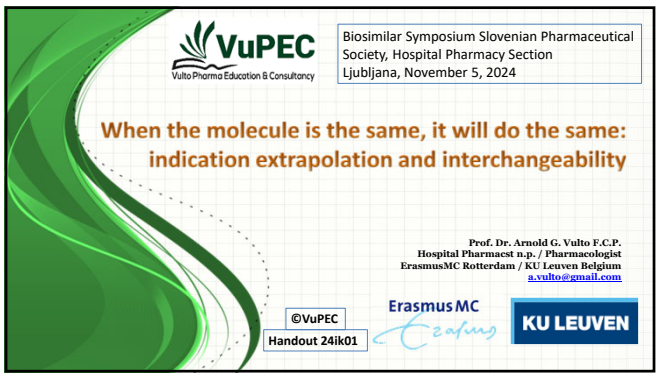
Povzetek

Razvoj podobnih bioloških zdravil temelji na dokazovanju, da se kandidat za podobno biološko zdravilo obnaša kot izdelek, ki posnema izvirnik (referenčni) izdelek. To se izvaja s kemičnimi, fizikalnimi in (kliničnimi) farmakološkimi tehnikami. Ta »postopek za podobno biološko zdravilo« se osredotoča na ključne lastnosti kakovosti (CQA), tiste lastnosti, ki so pomembne za učinkovitost in varnost (odsotnost neželenih učinkov) zdravila, vključno z imunogenostjo. Ko je podobnost dokazana, lahko pričakujemo, da se bo molekula obnašala enako pri vseh indikacijah, ki temeljijo na istem mehanizmu delovanja (kot je zaviranje TNF-alfa). Za regulatorje zadostuje klinična študija pri bolnikih z »najbolj občutljivo indikacijo« in z merili, ki lahko pokažejo morebitne razlike v aktivnosti, če te obstajajo. Naslednji korak je, da sponzor na podlagi literature ali z navajanjem referenčnega izdelka dokumentira ključne dejavnike za učinkovitost in varnost pri drugih indikacijah. Ti argumenti so pregledani s strani regulatornih agencij, in če so sprejeti kot znanstveno utemeljeni, se odobri ekstrapolacija na indikacije, ki niso bile testirane v formalni klinični študiji. Ko je izdelek registriran, je povsem običajno, da se podobno biološko zdravilo lahko predpisuje izmenično z izvirnim izdelkom in tudi z drugimi podobnimi biološkimi zdravili, ki se sklicujejo na isti referenčni izdelek.

Abstract

Developping biosimilars is all around proving that the candidate-biosimilar behaves as a look-alike of the innovator (reference) product. This is done with chemical, physical, and (clinical) pharmacological techniques. This »biosimilar exercise« is all about critical quality attributes (CQA), those attributes that matter for efficacy and safety (absence of side effects), of a medicine, including immuniogenicity. Once the similarity has been proven, one might expect that the molecule will behave the same in all indications that are based on the same mechanism of action (like TNF-alfa inhibition). For regulators suffice a clinical test in patients with »the most sensitive indication« and with endpoints that are able to show any difference in activity, if this exists. The next step is that the sponsor documents – based on literature or referring to the refence product - the critical factors for efficacy and safety in the other indications. These arguments are examined by the regulatory agencies, and if accepted as being scientifically justified, the extrapolation to indications that have not been tested in a formal clinical trial will be granted. Likewise, when the product has been licensed, it is just natural that the biosimilar can be prescribed interchangeably with the originator product and also with other biosimilars referring to the same reference product.

Reference: Weise et al. Blood 124(2014)3191 Biosimilars: the science of extrapolation.


VuPEC
Vulto Pharma Education & Consultancy
Biosimilar Symposium Slovenian Pharmaceutical Society, Hospital Pharmacy Section
Ljubljana, November 5, 2024
When the molecule is the same, it will do the same: indication extrapolation and interchangeability
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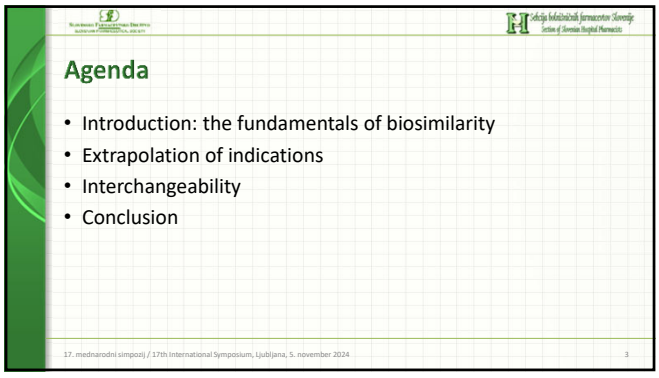
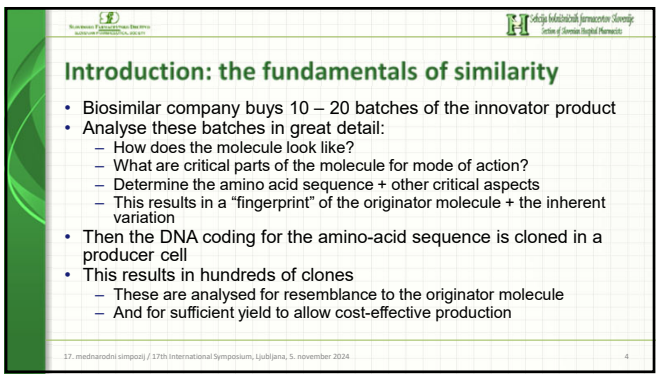

Agenda
• Introduction: the fundamentals of biosimilarity
• Extrapolation of indications
• Interchangeability
• Conclusion
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
3


Introduction: the fundamentals of similarity
• Biosimilar company buys 10 – 20 batches of the innovator product
• Analyse these batches in great detail:
– How does the molecule look like?
– What are critical parts of the molecule for mode of action?
– Determine the amino acid sequence + other critical aspects
– This results in a "fingerprint" of the originator molecule + the inherent variation
• Then the DNA coding for the amino-acid sequence is cloned in a producer cell
• This results in hundreds of clones
– These are analysed for resemblance to the originator molecule
– And for sufficient yield to allow cost-effective production
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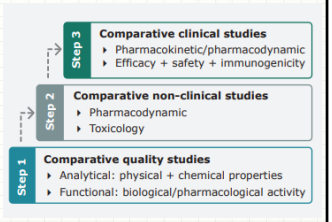
In theory, a stepwise approach in the development of biosimilars (in practice much in parallel)

1. Technical qualifications of reference product (including variation). This sets specifications for biosimilar candidate
2. Bioassays (for instance, on human cells)
3. Non-clinical tests in animals: by most agencies now seen as redundant
4. At least 1 clinical test in humans: one PK/PD, and if needed a patient trial in the most sensitive population with sensitive endpoints (i.e. *able to detect a difference* if there is one)
5. Specific post-marketing surveillance ("*Risk Management Plan*"), e.g. check for unexpected immunogenicity

The cornerstone of biosimilar development comparability studies

- **Extensive comparison** with the reference medicine
- **Well-established scientific principle** - evaluation of manufacturing changes during product life cycle
- Step-wise approach
- Assessment on the **totality of evidence** for similarity



Clinical development for biosimilars

Goal clinical studies in the context of biosimilar development

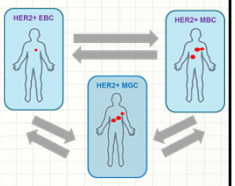
- Not needed to demonstrate *de novo* efficacy and safety of the product - therapeutic benefit already established for RP; goal = **Confirm biosimilarity** to the RP
- Ensure **no clinically meaningful differences** in efficacy, safety, immunogenicity – tailored to **detect clinically meaningful differences** between products **if these would be present**
- Final step **totality of evidence,** stepwise reduction of **residual uncertainty**

- The idea is, that if biosimilars behave the same in the most sensitive indication (to detect a difference), that this absence of difference will be the same in other indications based on the same mechanism of action.
- This most sensitive indication may well be different from the trials performed with the reference product

Extrapolation of indications

= Approval for one or more indications for which the RP is approved, without being subjected to clinical testing in all these indications itself

- Well established regulatory principle → **avoid unnecessary clinical trials**
- Granted based on **totality of evidence** for similarity and **scientific justification** (mechanism of action is the same, testing in relevant study population)
- Can be perceived as challenging for prescribers (e.g., when extrapolating between different therapeutic areas) if they have no knowledge about the biosimilar paradigm, butit is an **essential component** of the biosimilarity pathway



Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. **Biosimilars: the science of extrapolation.** Blood. 2014;124:3191–6.

EMA principles for indication extrapolation

- Efficacy and safety in extrapolated indications has to be scientifically justified
  - (not a free ride; that's why we see differences in labels)
  - Confidence in clinical experience with the reference product
  - Mechanism of action in each indication should be the same
    - With similar patient factors (comorbidities, co-medication, immunogenicity)
  - The degree to which functional moieties in the molecule can be characterised (e.g. with similar target receptors)
  - Etc.

Selection of sensitive endpoints for biosimilar trastuzumab clinical trials

Primary endpoint may be different to those used for approval of the RP

Preferred endpoints for demonstrating efficacy (new product)	Recommended endpoints for demonstrating biosimilarity

• A clinical endpoint that measures **survival**
  • Overall survival (OS)
  • Disease-free survival (DFS)
  • Progression-free survival (PFS)
• **May be not feasible/sensitive** enough to demonstrate biosimilarity of a biosimilar mAb to the reference product
	• A clinical endpoint that measures shorter-term **activity**
	  • **Overall response rate (ORR)**
	  • Partial + complete response
	  • In metastatic setting
	  • **Pathologic complete response (pCR)**
	  • In neoadjuvant + adjuvant setting
	  • Breast pCR or total pCR (breast + lymph nodes)

Barbier, L., *et al.* Br J Cancer 121, 199–210 (2019)

Example 2: infliximab

Active Substance	Brand Name	Approval Date
Infliximab (CT-P13)	Inflectra Remsima	September 2013 September 2013

Approved indications

Trial supported
- Ankylosing spondylitis
- Rheumatoid arthritis

Extrapolated
- Crohn's disease
- Psoriatic arthritis
- Psoriasis
- Ulcerative colitis

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Clinical and epidemiological research

EXTENDED REPORT

A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

Won Park,[1] Pawel Hrycaj,[2] Slawomir Jeka,[3] Vo
Pedro Miranda,[6] Helena Mikazane,[7] Sergio Gu
Yeon-Ah Lee,[9] Sang Joon Lee,[10] HoUng Kim,[

2 x 125 patients
Result: biosimilar almost identical

Clinical and epidemiological research

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Dae Hyun Yoo,[1] Pawel Hrycaj,[2] Pedro Miranda,[3] Edgar Ramiterre,[4] Mariusz Piotrowski,[5] Sergii Shevchuk,[6] Volodymyr Kovalenko,[7] Nenad Prodanovic,[8] Mauricio Abello-Banfi,[9] Sergio Gutierrez-Ureña,[10] Luis Morales-Olazabal,[11] Michael Tee,[12] Renato Jimenez,[13] Omid Zamani,[14] Sang Joon Lee,[15] HoUng Kim,[16] Won Park,[17] Ulf Müller-Ladner[18]

2 x 300 patients
Result: biosimilar at least equal with reference product
Total: 54 weeks

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Interchangeabilty

- EMA: on a population level the outcome of treatment with a biosimilar or reference product will be the same.
  - Has no legal meaning in memberstates
- FDA: a legal designation
  - Is not "a better" biosimilar: quality, efficacy and safety are te same
  - Is needed with respect to some state pharmacy ruling
- This difference between EU and US has caused a lot of confusion

The confusing terminology

- **Interchangeability**: EMA differs fundamentally from FDA
  - Very confusing: population versus individual level
- **Switching** is both:
  - Change from one treatment / molecule to another
  - Change from reference product to biosimilar
    (also confusingly coined *non-medical switching*).
  - Maybe better word **transitioning**: only for biosimilars (Dörner, 2016)
- **Substitution**:
  - Dispensing another drug as prescribed without consulting the prescriber
  - Why discuss? We generally don't do it (with few exceptions).

Weise et al. Nature Biotechnology 29, 690–693 (2011)
Dörner et al Ann Rheum Dis doi:10.1136/annrheumdis-2016-209166

Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective

Pekka Kurki[1] · Sean Barry[2] · Ingrid Bourges[3] · Panagiota Tsantili[4] · Elena Wolff-Holz[5]

Abstract
Background Biosimilars have been used for 15 years in the European Union (EU), and have been shown to reduce costs and increase access to important biological medicines. In spite of their considerable exposure and excellent safety record, many prescribers still have doubts on the safety and interchangeability of biosimilars, especially monoclonal antibodies (mAbs) and fusion proteins.
Objectives The aim of this study was to analyse the short- and long-term safety and interchangeability data of bi mAbs and fusion proteins to provide unbiased information to prescribers and policy makers.
Methods Data on the safety, immunogenicity and interchangeability of EU-licensed mAbs and fusion proteins wer ined using European Public Assessment Reports (EPARs) and postmarketing safety surveillance reports from the E Medicines Agency (EMA). As recent biosimilar approvals allow self-administration by patients by the subcutaneou the administration devices were also analyzed.
Results Prelicensing data of EPARs (six different biosimilar adalimumabs, three infliximabs, three etanercepts, thre mabs, two bevacizumabs, and six trastuzumabs) revealed that the frequency of fatal treatment-emergent adverse (TEAEs), TEAEs leading to discontinuation of treatment, serious adverse events (SAEs), and main immune-mediated events (AEs) were comparable between the biosimilars and their reference products. The availability of new biosimil entations and administration devices may add to patient choice and be an emerging factor in the decision to switch Analysis of postmarketing surveillance data covering up to 7 years of follow-up did not reveal any biosimilar-specific effects. No product was withdrawn for safety reasons. This is in spite of considerable exposure to biosimilars in tre naive patients and in patients switched from the reference medicinal product to the biosimilar. Analysis of data from st studies provided in regulatory submissions showed that single or multiple switches between the originator and its bi versions had no negative impact on efficacy, safety or immunogenicity.
Conclusions In line with previous reports of prelicensing studies of biosimilar mAbs and etanercepts, this study demo comparable efficacy, safety, and immunogenicity compared with the reference products. This is the first study to com sively analyze postmarketing surveillance data of the biosimilar mAbs and etanercept. An analysis of more than 1 patient-treatment years of safety data raised no safety concerns. Based on these data, we argue that biosimilars appr the EU are highly similar to and interchangeable with their reference products. Thus, additional systematic switch are not required to support the switching of patients.

- Study of short- and long-term safety and interchangeability data of biosimilar mAbs and fusion proteins
- Analysis of ***more than 1 million patient-treatment years*** of safety data raised no safety concerns.
- Based on these data, we argue that biosimilars approved in the EU are highly similar to and interchangeable with their reference products.
- Additional systematic switch studies are not required to support the switching of patients
- Drugs 81(2021)1881

Biosimilar interchangeability

EUROPEAN MEDICINES AGENCY

HMA Heads of Medicines Agencies

Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU

Biosimilars approved in the EU are interchangeable (21 April 2023)

*HMA and EMA consider that **once a biosimilar is approved in the EU it is interchangeable**, which means the biosimilar can be used instead of its reference product (or vice versa) or one biosimilar can be replaced with another biosimilar of the same reference product.*

***Decisions on how to implement interchangeability** either through **switching** (under the control of the prescriber) **and/or substitution** (the practice of dispensing one medicine instead of another medicine without consulting the prescriber, such as automatic substitution at the pharmacy level), are not within the remit of EMA and are **managed by individual member states**.*

https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

Supported by a massive real-world-evidence (between 2006 – 2021)

5.8 billion

patient treatment days

With EU approved biosimilar medicines since 2006

26

Conclusion

- Based on scientific pharmacological principles and extensive trial-experience + real world evidence we can:
  - Allow extrapolation of indications
    - (use a biosmilar in an indication not supported by a dedicated patient trial)
  - Use a reference product and its biosimilars interchangeably
    - Allowing the use of the most cost-effective product
- Hospital pharmacists have to include these principles in their education to raise trust in biosimilar prescribing

17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024 27

Podobna biološka zdravila: izkušnje s področja hematologije

Biosimilars: Experiences in Hematology

Matjaž Sever

Univerzitetni klinični center Ljubljana, Klinični oddelek za hematologijo

Povzetek

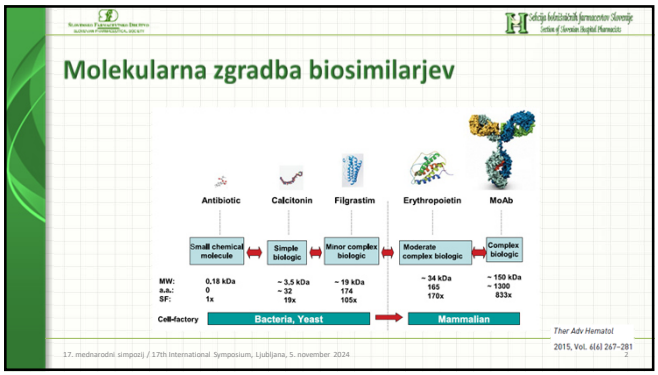
Biološka zdravila so ključna v hematologiji za zdravljenje različnih krvnih bolezni, kot so levkemije, limfomi in anemije. Podobna biološka zdravila (PBZ) so zelo podobna že odobrenim biološkim zdravilom in so klinično enakovredna originalnim zdravilom. Uporaba PBZ omogoča dostop do učinkovitih terapij po nižjih stroških, kar izboljša dostopnost zdravljenja za bolnike. PBZ so podvržena obsežnim primerjalnim študijam, da se zagotovi njihova varnost, učinkovitost in kakovost. V hematologiji se biološko podobna zdravila uporabljajo za zdravljenje različnih krvnih bolezni. Filgrastim je primer biološko podobnega zdravila, ki se uporablja za spodbujanje proizvodnje nevtrofilcev pri bolnikih z nevtropenijo. Rituksimab se uporablja za zdravljenje nekaterih vrst limfoma in kronične limfocitne levkemije. Epoetin alfa se uporablja za zdravljenje anemije pri bolnikih s kronično ledvično boleznijo, mielodisplastičnim sindromom ali pri tistih, ki prejemajo kemoterapijo.

Abstract

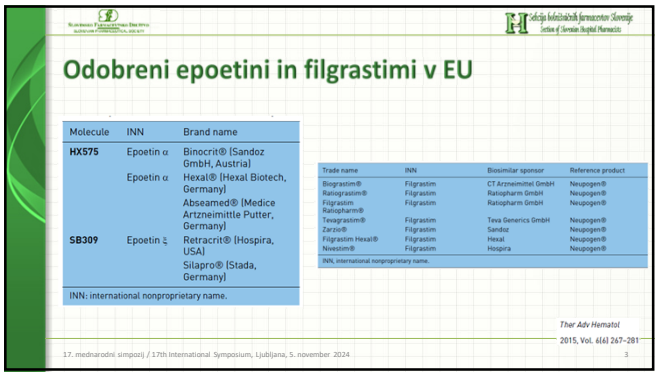
Biological drugs are essential in hematology for the treatment of various blood diseases, such as leukemias, lymphomas, and anemias. Biosimilar medicines (BSMs) are highly similar to already approved biological medicines and are clinically equivalent to the original drugs. The use of BSMs allows access to effective therapies at lower costs, improving treatment accessibility for patients. BSMs undergo extensive comparative studies to ensure their safety, efficacy, and quality. In hematology, biosimilar medicines are used to treat various blood diseases. Filgrastim is an example of a biosimilar medicine used to stimulate the production of neutrophils in patients with neutropenia. Rituximab is used to treat certain types of lymphoma and chronic lymphocytic leukemia. Epoetin alfa is used to treat anemia in patients with chronic kidney disease, myelodysplastic syndrome, or those receiving chemotherapy.


Podobna biološka zdravila: izkušnje s področja hematologije
Matjaž Sever

1


Molekularna zgradba biosimilarjev
Antibiotic
Calcitonin
Filgrastim
Erythropoietin
MoAb
Small chemical molecule
Simple biologic
Minor complex biologic
Moderate complex biologic
Complex biologic
MW: 0,18 kDa ~ 3,5 kDa ~ 19 kDa ~ 34 kDa ~ 150 kDa
a.a.: 0 ~ 32 174 165 ~ 1300
SF: 1x 19x 105x 170x 833x
Cell-factory
Bacteria, Yeast
Mammalian
Ther Adv Hematol
2015, Vol. 6(6) 267–281
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
2

2


Odobreni epoetini in filgrastimi v EU
Molecule INN Brand name
HX575 Epoetin α Binocrit® (Sandoz GmbH, Austria)
Epoetin α Hexal® (Hexal Biotech, Germany)
Abseamed® (Medice Artzneimittle Putter, Germany)
SB309 Epoetin ξ Retracrit® (Hospira, USA)
Silapro® (Stada, Germany)
INN: international nonproprietary name.
Trade name INN Biosimilar sponsor Reference product
Biograstim® Filgrastim CT Arzneimittel GmbH Neupogen®
Ratiograstim® Filgrastim Ratiopharm GmbH Neupogen®
Filgrastim Ratiopharm® Filgrastim Ratiopharm GmbH Neupogen®
Tevagrastim® Filgrastim Teva Generics GmbH Neupogen®
Zarzio® Filgrastim Sandoz Neupogen®
Filgrastim Hexal® Filgrastim Hexal Neupogen®
Nivestim® Filgrastim Hospira Neupogen®
INN, international nonproprietary name.
Ther Adv Hematol
2015, Vol. 6(6) 267–281
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
3

3

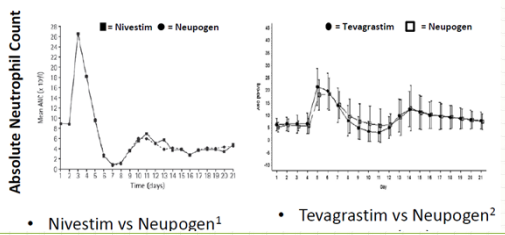
Filgrastim

- - Biosimilar filgrastim (Sandoz) je bil odobren v Evropi leta 2009 in v ZDA leta 2015, ko je postal prvi biosimilar, ki ga je odobrila ameriška FDA.
- - Klinične študije faze III so bile izvedene pri bolnikih z rakom dojke, ki so prejemali mielosupresivno kemoterapijo.
- - Odobritev je bila nato podeljena za vse indikacije referenčnega biološkega zdravila na podlagi ekstrapolacije.
- - Ekstrapolacija je dobro sprejeta v razvoju bioloških zdravil in regulativnih kontekstih.
- - Več kot desetletje kliničnih izkušenj od odobritve podpira celovitost dokazov glede učinkovitosti in varnosti biosimilarja filgrastima.

BioDrugs (2019) 33:635–645

4

Filgrastim



- Nivestim vs Neupogen[1]
- Tevagrastim vs Neupogen[2]

1. Waller CF, et al. *Oncologie*. 2010;13(10):504-511.
2. Gatzemeier U, et al. *J Thorac Oncol*. 2009;4(6):736-740.

5

Pegfilgrastim

- Pegfilgrastim se je izkazal za bolj učinkovitega od filgrastima pri zmanjševanju kemoterapije povezane nevtropenije in pri doseganju ciljne intenzivnosti odmerka, saj je slednji pogosto premalo odmerjen v klinični praksi.
- Uporaba biosimilarnega pegfilgrastima olajša dostop in, podprta s smernicami in kliničnimi rezultati, omogoča uresničitev celotnega potenciala pegfilgrastima po nižjih stroških.

Brand name	Manufacturer	Registration trial	EMA approval	FDA approval
Pelgraz®	Accord Healthcare	Drost et al. 2018 [56] Phase III randomised, assessor-blinded, multicentre study on 389 breast cancer patients with reference arms of US-Neulasta and EU-Neulasta	September 2018	
Udenyca®	Coherus	Dose-response trial*	September 2018	November 2018
Fulphila®	Mylan	Waller et al. 2019 [57] Phase III randomised, assessor-blinded study on 194 breast cancer patients with reference arm of EU-Neulasta	November 2018	June 2018
Pelmeg®	Cinfa Biotech/Mundipharma	Dose-response trial*	November 2018	
Ziextenzo®	Sandoz	Harbeck et al. 2016 [58] Phase III randomised, assessor-blinded, multicentre study on 181 breast cancer patients with reference arm of EU-Neulasta	November 2018	November 2019
Grasustek®	Juta Pharma	Grasustek (EPAR)† Phase III randomised, assessor-blinded, multicentre study on 254 breast cancer patients with reference arm of EU- Neulasta	April 2019	
Pegfilgrastim Mundipharma®	Mundipharma	Dose-response trial*	December 2019	

BioDrugs (2020) 34:255–263

6

Pegfilgrastim

Clinical benefits vs filgrastim (<7 days)	Economic benefits vs reference pegfilgrastim
Reduced FN incidence	Cost savings > 30%
Reduced FN-related hospitalisations	Increased patient access
Reduced chemotherapy dose delays	Create additional budget for new medicines
Improved relative dose intensity	Financial sustainability
Improved adherence to G-CSF guidelines	Improved device/additional handling features
Reduced hospital visits and risk of nosocomial infections	
Improved patient acceptability and adherence	

BioDrugs (2020) 34:255–263

7

Pegfilgrastim

- Primarna profilaksa z G-CSF je ključna za bolnike na kemoterapijah z visokim tveganjem (≥ 20%) ali srednjim tveganjem (10–20%) in dodatnimi dejavniki tveganja.
- Zagotavlja ohranjanje intenzivnosti odmerka terapije, kar izboljšuje preživetje bolnikov z rakom.
- Pegfilgrastim je boljši od filgrastima pri zmanjševanju nevtropenije in FN, izboljšanju skladnosti s smernicami G-CSF in doseganju ciljne RDI.
- Biosimilarni pegfilgrastim ponuja novo priložnost za ponoven razmislek o vodenju nevtropenije.
- Pomembne klinične in ekonomske koristi.
- Skupno, multidisciplinarno delovanje, ki vključuje predpisujoče zdravnike, onkološke medicinske sestre in farmacevte, podprto s smernicami in kliničnimi pravili, bo omogočilo uresničitev celotnega potenciala te pomembne terapije.

BioDrugs (2020) 34:255–263

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Biosimilarji na področju presaditve

Original biologic	Biosimilars approved[a]	Year of approval (regulatory body)	Approved/ possible uses in HCT
Filgrastim	Tevagrastim	2008 (EMA)	–Mobilization of stem cells for auto-HCT[a]
	Ratiograstim	2008 (EMA)	
	Filgrastim Hexal	2009 (EMA)	
	Zarzio	2009 (EMA)	–Mobilization of stem cells in allo-HCT donors
	Accofil	2014 (EMA)	
	Zarxio	2015 (US-FDA)	
	Nivestim	2010(EMA)	
	Grastofil	2013 (EMA)	–Cell recovery after transplant
	Nivestym	2018 (US-FDA)	
Rituximab	Truxima	2017 (EMA);	–Chronic GVHD therapy
	Rixathon	2018 (US-FDA)	
	Riximyo	2017 (EMA)	–Chronic GVHD prevention
	Blitzima	2017 (EMA)	
	Rituzena	2017 (EMA)	
		2017 (EMA)	
Infliximab	Inflectra	2013 (EMA);	–Acute GVHD therapy
	Flixabi	2016 (US-FDA)	
	Remsima	2016 (EMA)	–Acute GVHD prevention
	Renflexis	2013 (EMA)	
	Ixifi	2017 (US-FDA)	
	Zessly	2017 (US-FDA)	
		2018 (EMA)	
Etanercept	Benepali	2016 (EMA)	–Acute GVHD therapy
	Erelzi	2016 (US-FDA);	
		2017 (EMA)	–Therapy for BOS and IPS.

Bone Marrow Transplantation (2020) 55:698–707

9

Biosimilarji na področju presaditve

References	Type of Transplant	Biosimilar	Dose (µg/kg/day)	MM	NHL	HL	AML / ALL	GCT
Publicover A. et al. (2013)	Auto	Ratiograstim®/ Ref. G-CSF + Chemo	NA	76	65	13	-	-
Kircheer H. (2011)	Auto	Ratiograstim® + Chemo	NA	7	11	1	-	1
Sammassimo S. et al. (2011)	Auto	Tevagrastim® + Chemo	300µg/ day	6	8	1	-	-
Sever M. et al. (2012)	Auto	Tevagrastim®	10	-	-	-	-	-
Andreola G. et al. (2012)	Auto	Tevagrastim® + Pleri + Chemo	10	8	4	2	-	-
Lanza F. et al. (2012)	Auto	Tevagrastim® + Pleri + Chemo	NA	81	105	25	-	-
Lazlo D. et al. (2012)	Auto	Ref. G-CSF / Tevagrastim® + Pleri + Chemo	10	10	10	1	-	-
Morabito L. et al. (2012)	Auto	Ref. G-CSF / Tevagrastim® + Pleri	10	3	1	-	-	-
Total				191	204	43	-	1

Schmidt M et al. Theranostics. 2014; 4: 280–289 10

10

Rituximab

- Uporablja se tudi pri revmatoidnem artritisu, kjer so B limfociti vključeni v vnetje sklepov, ter pri granulomatozi s poliangiitisom (GPA) in mikroskopski poliangiitis (MPA), kjer uničenje B limfocitov zmanjša proizvodnjo protiteles, ki napadajo krvne žile in povzročajo vnetje.
- Obstajajo štirje možni mehanizmi delovanja anti-CD20 protiteles za uničenje B celic: (i) ADCC, (ii) CDC, (iii) apoptoza in (iv) fagocitoza malignih B celic.
- V klinični praksi se mehanizmi delovanja lahko razlikujejo glede na indikacijo.
- Do leta 2019 je bilo v EU licenciranih sedem biosimilarjev rituksimaba, ki vključujejo GP2013 (Sandoz) in CT-P10 (Celltrion).
- Biosimilarji so bili testirani v različnih kliničnih indikacijah, EMA pa je odobrila vse indikacije referenčnega izdelka.

HemaSphere (2019) 3:6(e322) 11

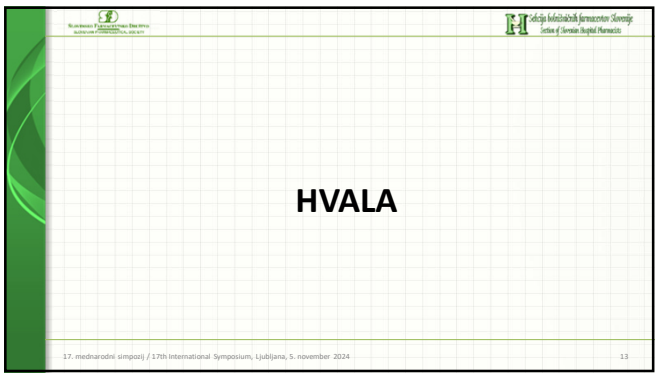
11

Rituximab

- Licenciranje bioloških zdravil je v Evropi centralizirano, kar omogoča prosti pretok licenciranih zdravil med državami EU.
- Sprejemanje biosimilarjev rituksimaba s strani predpisovalcev je bilo v Evropi relativno gladko po uvedbi TNF-alfa inhibitorjev infliksimaba in etanercepta.
- V nekaterih državah, kot je Nizozemska, je bilo v treh mesecih po uvedbi 90% bolnikov prevedenih na biosimilarje.
- Hematologi so že bili seznanjeni z biosimilarji - hematologija je bolj laboratorijsko usmerjena specialnost kot mnoge druge.

HemaSphere (2019) 3:6(e322) 12

12


HVALA
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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13

Podobna biološka zdravila: izkušnje s področja gastroenterologije in zdravljenja kronične vnetne črevesne bolezni

Biosimilars: Experiences in Gastroenterology and the Treatment of Chronic Inflammatory Bowel Disease

David Drobne

Univerzitetni klinični center Ljubljana, Klinika za gastroenterologijo

Povzetek

Podobna biološka zdravila smo privzeli za zdravljenje kronične vnetne črevesne bolezni v UKC Ljubljana med prvimi v Sloveniji in Evropi. Predstavil bom našo izkušnjo z infliximabom, ki je bilo prvo biološko zdravilo za področje kronične vnetne črevesne bolezni, kjer smo praktično čez noč napravili prehod iz originatorja na podobno biološko zdravilo. Predstavil bom bolnika z značilnim nocebo učinkom in zakaj je pomembno, da je t.i. »non-medical switch« vseeno vsaj malo tudi »medical«. Predstavil bom tudi aktualne podatke o rabi podobnih bioloških zdravil iz Registra kronične vnetne črevesne bolezni.

Abstract

At the University Medical Centre Ljubljana, we were among the first in Slovenia and Europe to introduce biosimilar drugs for the treatment of chronic inflammatory bowel disease. I will present our experience with infliximab, the first biosimilar drug for chronic inflammatory bowel disease, where we practically made an overnight switch from the originator to the biosimilar. I will present a case of a patient with a characteristic nocebo effect and explain why it is important that a so-called "non-medical switch" is at least somewhat "medical". I will also present current data on the use of biosimilar drugs from the Chronic Inflammatory Bowel Disease Registry.

Podobna biološka zdravila:

izkušnje s področja gastroenterologije
in zdravljenja kronične vnetne črevesne bolezni

doc. dr. David Drobne, dr.med.

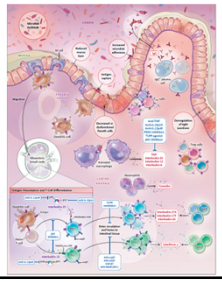
Univerzitetni klinični center Ljubljana, Klinika za gastroenterologijo

5. november 2024, Domus Medica,

1

Kaj je kronična vnetna črevesna bolezen?

- idiopatsko, kronično vnetje prebavil
- ločimo dve glavni obliki
  - Crohnova bolezen
  - Ulcerozni kolitis
  - neklasificirani kolitis



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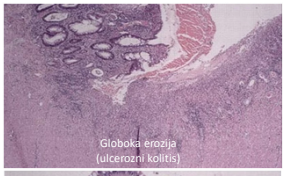

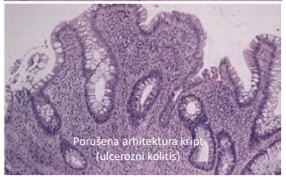

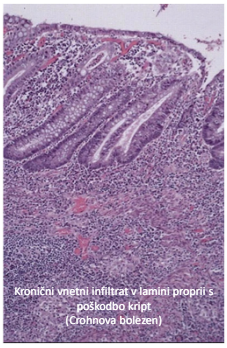

Odze Modern Pathology 2003:347-358.

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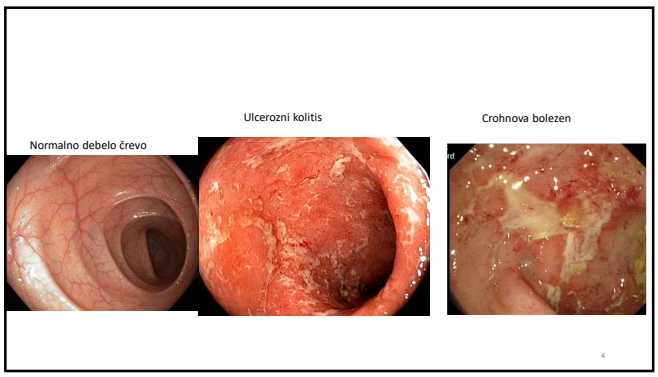
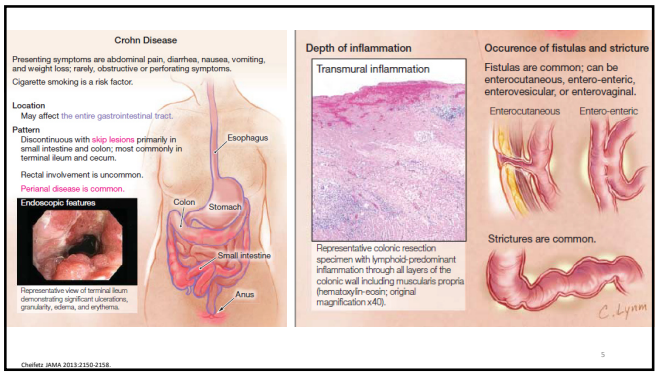
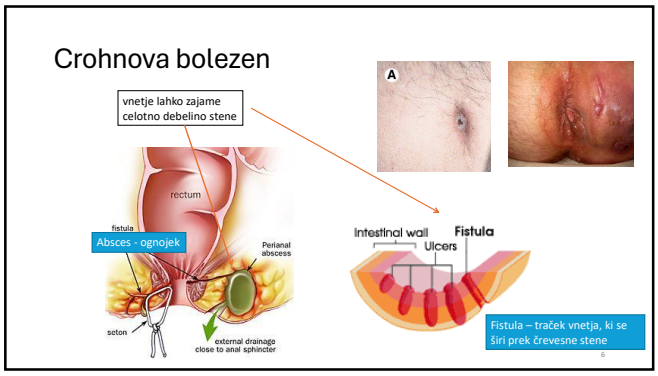

Ulcerozni kolitis
Crohnova bolezen
Normalno debelo črevo

4

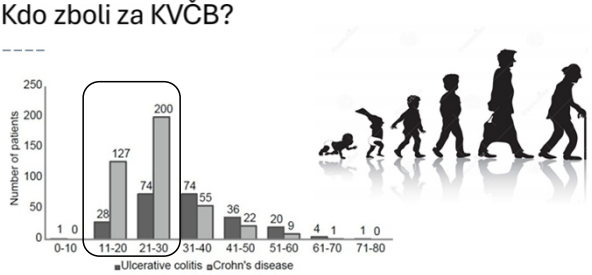

Crohn Disease
Presenting symptoms are abdominal pain, diarrhea, nausea, vomiting, and weight loss; rarely, obstructive or perforating symptoms.
Cigarette smoking is a risk factor.
Location
May affect the entire gastrointestinal tract.
Pattern
Discontinuous with skip lesions primarily in small intestine and colon; most commonly in terminal ileum and cecum.
Rectal involvement is uncommon.
Perianal disease is common.
Endoscopic features
Representative view of terminal ileum demonstrating significant ulcerations, granularity, edema, and erythema.
Esophagus
Stomach
Colon
Small intestine
Anus
Depth of inflammation
Transmural inflammation
Representative colonic resection specimen with lymphoid-predominant inflammation through all layers of the colonic wall including muscularis propria (hematoxylin-eosin; original magnification x40).
Occurence of fistulas and stricture
Fistulas are common; can be enterocutaneous, entero-enteric, enterovesicular, or enterovaginal.
Enterocutaneous
Entero-enteric
Strictures are common.
C.Lynn
Cheifetz JAMA 2013;2150-2158.

5


Crohnova bolezen
vnetje lahko zajame celotno debelino stene
A
rectum
fistula
Absces - ognojek
Perianal abscess
seton
external drainage close to anal sphincter
Intestinal wall
Ulcers
Fistula
Fistula – traček vnetja, ki se širi prek črevesne stene

6

Kdo zboli za KVČB?



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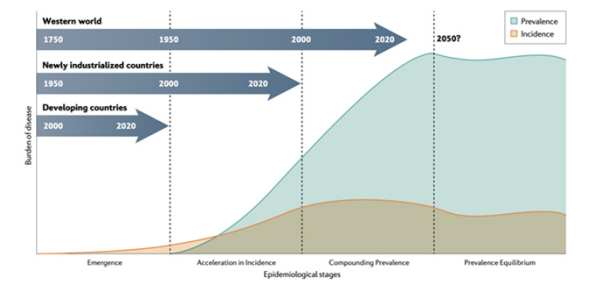

Kaplan, Gilaad G, and Joseph W Windsor. "The four epidemiological stages in the global evolution of inflammatory bowel disease." *Nature reviews. Gastroenterology & hepatology* 2021

8

Epidemiološki podatki za Slovenijo

INCIDENCA	UK	CB	Skupna incidenca KVČB vključno z nKVČB
od leta 1990 do 2000	4,6/100.000 (95% CI:2,7 – 6,4)	3,8/100.000 (95% CI:2,6 – 5,1)	8,7/100.000 (95% CI:6,3 – 11,2)
od leta 2001 do 2012	8,9/100.000 (95% CI:6,9 – 10,8)	7,4/100.000 (95% CI:5,6 – 9,3)	18,2/100.000 (95% CI:15,1 – 21,3)
od leta 1990 do 2012	6,8/100.000 (95% CI:5,2 – 8,4)	5,7/100.000 (95% CI:4,4 –7,1)	13,7/100.000 (95% CI:10,9 – 16,6)

Epidemiološka študija dr. Barage, l. 2013

Rast 13% - 14% letno
cca **8000** bolnikov v Sloveniji

UR-CARE:
register bolnikov s KVČB

9

Klinični oddelek za gastroenterologijo

2016: Med prvimi začnemo z uporabo podobnih bioloških zdravil

Obvestilo lekarne:
zdravilo Ramicade (originator infliximab) ne bo več na voljo, potrebno je preklopiti vse bolnike na biosimilar (čez noč)

10

LETO 2016

- UKC LJ: odločitev o menjavi originatorja infliximab za biosimilar
- Nujna menjava
- Izjeme lahko bolniki, ki niso v remisiji

11

Zakaj je bilo to za nas presenečenje?

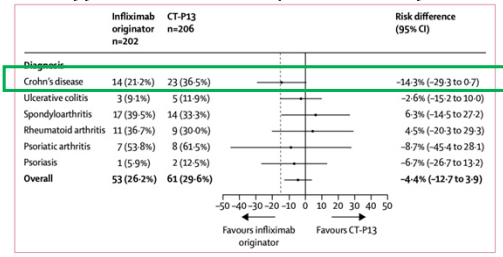

Figure 2: **Forest plot of risk difference according to disease**
Figure shows data for the per-protocol set. Risk difference is adjusted for treatment duration of infliximab originator at baseline.

Jorgensen Lancet 2017

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Tranzicija skozi leta KVČB: 2016 do 2018

Datum	Vsi bolniki na biol. terapiji	Humira	Ramicade	Simponi	Remsima	Entyvio	Stelara
12/16	344	125	128	10	38	30	13
12/17	448	142	17	19	172	63	35
4/18	492	138	18	15	177	82	62

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LETO 2018: infliximab biosimilar
177 bolnikov s KVČB

Novi bolniki (biosimilar kot prvo zdravilo): 94

Non-medical switch: 83

14

Outcome of non-medically switched patient with IBD (2018):

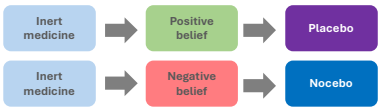
In total 115 pt:

- Still on biosimilar 83
- Discontinued: 32
  1. Back to reference IFX: 14
     (disease flare, worsening skin lesions, arthralgia, open fistula, diarhea, hair loss, etc)
  2. Vedolizumab: 5
  3. Ustekinumab: 4
  4. Discontinued: 4 (operation, remision, etc)
  5. Adalimumab: 2
  6. Other institution: 3

15

The nocebo phenomena: the negative equivalent of placebo

Placebo vs. nocebo



- **Nocebo effect**: the induction or the worsening of symptoms induced by sham or active therapies[1,2]
- **Nocebo response**: new and worsening symptoms that are caused only by negative expectations on the part of the patient and/or negative verbal and non-verbal communications on the part of the treating person, without any (sham) treatment[1]

1. Häuser W, et al. *Dtsch Arztebl Int* 2012;109:459–65;
2. Planès S, et al. *Pharmacol Res Perspect* 2016;4:e00208.

16

Leto 2024

- UKC LJ KVČB:
  - Biosmilarji infliksimaba zdravilo izbora
  - Biosimiarji adalimumaba zdravilo izbora
  - Biosimilarji ustekinumaba: obdobje prehoda

17

Crohnova bolezen: razmerje originator/biosmilar Slovenija – podatki iz registra za leto 2023

Utilisation of advanced treatments in inflammatory bowel disease in Slovenia – national report from UR-CARE Registry for the year 2023

Uporaba naprednih zdravil pri bolnikih s kronično vnetno črevesno boleznijo v Sloveniji – nacionalni podatki iz UR-CARE registra za leto 2023

Table 4. Number of patients, who remained on biologic in respective line of treatment for Crohn's disease (from inception of UR-CARE Registry)

Line	All	Adalimumab / biosimilars	Adalimumab / Humira	Certolizumab	Golimumab	Guselkumab	Infliximab/ biosimilars	Infliximab/ Remicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	713	119 (16,7%)	132 (18,5%)	0	0	0	149 (20,9%)	63 (8,8%)	1 (0,1%)	0	122 (17,1%)	127 (17,8%)
Second line	267	17 (6,4%)	28 (10,5%)	0	0	0	57 (21,3%)	7 (2,6%)	1 (0,4%)	0	139 (48,7%)	27 (10,1%)
Third line	116	2 (1,7%)	3 (2,6%)	0	0	0	18 (15,5%)	2 (1,7%)	0	0	68 (58,6%)	23 (19,8%)
Fourth line	50	3 (6,0%)	4 (8,0%)	0	0	0	7 (14,0%)	1 (2,0%)	0	0	24 (48,0%)	11 (22,0%)
Fifth line	14	1 (7,1%)	0	0	0	3 (21,4%)	3 (21,4%)	0	0	0	4 (28,6%)	3 (21,4%)
Sixth line	2	1 (50,0%)	0	0	0	0	0	0	0	0	0	1 (50,0%)
Sevent line	1	0	0	0	0	0	0	0	0	0	0	1 (100%)
Total*	1163	143 (12,3%)	167 (14,4%)	0	0	3 (0,3%)	234 (20,1%)	73 (6,3%)	2 (0,2%)	0	348 (29,9%)	193 (16,6%)

18

Ulcerozni kolitis: razmerje originator/biosmilar Slovenija – podatki iz registra za leto 2023

Utilisation of advanced treatments in inflammatory bowel disease in Slovenia – national report from UR-CARE Registry for the year 2023

Uporaba naprednih zdravil pri bolnikih s kronično vnetno črevesno boleznijo v Sloveniji – nacionalni podatki iz UR-CARE registra za leto 2023

Table 5. Number of prescriptions (treatment episodes) in respective lines of therapy for ulcerative colitis (from inception of UR-CARE Registry)

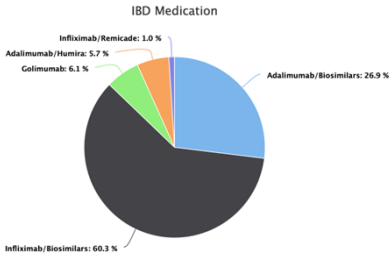
Line	All	Adalimumab / biosimilars	Adalimumab / Humira	Certolizumab	Golimumab	Guselkumab	Infliximab/ biosimilars	Infliximab/ Remicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	811	31 (3,8%)	59 (7,3%)	0	75 (9,2%)	0	191 (23,6%)	97 (12,0%)	0	0	55 (6,8%)	303 (37,4%)
Second line	327	13 (4,0%)	43 (13,1%)	0	13 (4,0%)	0	78 (23,9%)	25 (7,6%)	0	1 (0,3%)	39 (11,9%)	115 (35,2%)
Third line	151	4 (2,6%)	0	0	4 (2,6%)	0	30 (19,9%)	4 (2,6%)	0	3 (2,0%)	47 (31,1%)	51 (33,8%)
Fourth line	40	1 (2,5%)	8 (20,0%)	0	1 (2,5%)	0	7 (17,5%)	3 (7,5%)	0	0	19 (47,5%)	7 (17,5%)
Fifth line	11	0	0	0	2 (18,2%)	0	1 (9,1%)	4 (36,4%)	0	0	3 (27,3%)	1 (9,1%)
Sixth line	2	0	1 (50,0%)	0	0	0	0	0	0	0	1 (50,0%)	0
Seventh line	0	0	0	0	0	0	0	0	0	0	0	0
Total*	1343	49 (3,7%)	111 (8,3%)	0	95 (7,1%)	0	307 (22,9%)	134 (10,0%)	0	4 (0,3%)	164 (12,2%)	478 (35,6%)

19

UKC LJUBLJANA – izpis iz registra (okt 2024)

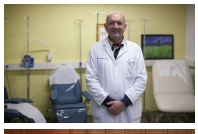
Prepisovanje od leta 2020 dalje

TNF zaviralci – biosimilarji 87.2%



20

IBD team LJUBLJANA



- 5 gastroenterology consultants
- 2-4 trainees
- 3 IBD nurses
- 2 study coordinators

21

Hvala za pozornost

22

Podobna biološka zdravila: izkušnje s področja onkologije

Biosimilars: Experience in Oncology

Simona Borštnar

Onkološki Inštitut Ljubljana

Povzetek

Biološka zdravila kot so tarčna monoklonska protitelesa so v zadnjih dveh desetletjih postala ena od ključih zdravil v onkologiji. Razvoj podobnih bioloških zdravil izhaja iz visokih stroškov bioloških zdravil. Podobna biološka zdravila, ki so po zgradbi in delovanju podobna referenčnim biološkim zdravilom so za bolnike enako učinkovita in varna, vendar cenejša. Imajo ključno vlogo pri spodbujanju konkurence v farmacevtski industriji in zagotavljanju dostopa bolnikov do osnovnih zdravil.

V onkologiji so trenutno na voljo tri podobna biološka zdravila iz skupine monoklonskih protiteles: trastuzumab, rituksimab in bevacuzimab. Od leta 2019 do sedaj se je skupen strošek za ta zdravila na Onkološkem inštitutu v Ljubljani, ki pokriva zdravljenje več kot 70% vseh slovenskih bolnikov z rakom, znižal za več kot trikrat z okoli 13 mio EUR na okoli 4 mio EUR. Prihodnost podobnih bioloških zdravil pri zdravljenju raka veliko obeta pri širjenju indikacij, saj bo več podobnih bioloških zdravil prejelo regulativno odobritev, njihova uporaba pa se bo verjetno razširila na širši spekter vrst raka in terapevtskih indikacij.

Abstract

Biological drugs, such as targeted monoclonal antibodies, have become one of the key treatments in oncology over the past two decades. The development of biosimilar drugs stems from the high costs of biological drugs. Biosimilar drugs, which are similar in structure and function to reference biological drugs, are equally effective and safe for patients but are less expensive. They play a crucial role in promoting competition in the pharmaceutical industry and ensuring patient access to essential medicines.

In oncology, there are currently three biosimilar drugs available from the monoclonal antibody group: trastuzumab, rituximab, and bevacizumab. From 2019 to the present, the total cost for these drugs at the Oncology Institute in Ljubljana, which covers the treatment of more than 70% of all Slovenian cancer patients, has decreased more than threefold from around 13 million EUR to around 4 million EUR. The future of biosimilar drugs in cancer treatment is very promising in terms of expanding indications, as more biosimilar drugs will receive regulatory approval, and their use is likely to extend to a broader range of cancer types and therapeutic indications.

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Podobna biološka zdravila: izkušnje s področja onkologije

Doc.dr. Simona Borštnar, dr. med
Oddelek za internistično onkologijo
Onkološki inštitut Ljubljana

Ljubljana, 5.11.2024

1

Razkritje

Avtorski honorarji za predavanja:
Astra Zeneca, Eli Lilly, Lek, MSD, Novartis, Pfizer, Roche, Swixx Biopharma
Svetovalni odbori in strokovna mnenja:
AstraZeneca, Gilead, Eli Lilly, MSD, Merck, Novartis, Pfizer, Roche, Swixx Biopharma

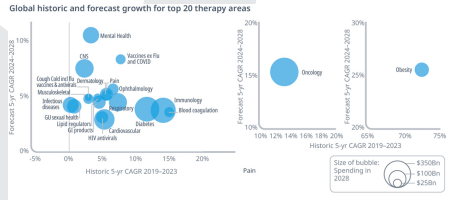
2

Vsebina

- Pregled naraščajočih stroškov za zdravila v onkologiji
- Biološka zdravila v onkologiji
- Biološka podobna zdravila v onkologiji
- Znižanje stroškov zdravljenja z uporabo bioloških podoibnih zdravil v onkologiji

3

Napoved rasti za 20 največjih terapevtskih področij



Source: Source: IQVIA Forecast Link, Dec 2023.
Notes: Bubble Size represents forecast in 2028; COVID Vaccine and therapeutics are not included. Oncology includes therapeutic oncology only and not supportive care. Immunology includes small molecule and biologic treatments for a range of diseases as noted. Neurology includes central nervous system disorder treatments and mental health treatments but does not include pain management or anesthesia. Pain includes narcotic and non-narcotic analgesics, muscle relaxants and migraine treatments. Cardiovascular includes hypertension and other cardiovascular treatments with the exception of lipid regulators, which are shown separately.
Report: Global Use of Medicines 2024: Outlook to 2028. IQVIA Institute for Human Data Science, January 2024.

CAGR= compound annual growth rate / letna spopnja rasti

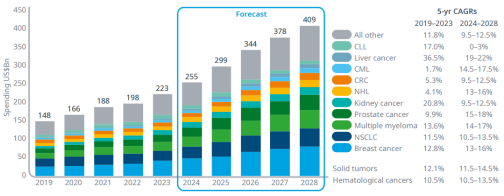
https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2024-outlook-to-2028

4

Porast stroškov po posameznih lokalizacijah raka do leta 2028

Six of the top 10 tumors have double-digit spending growth, all areas of significant numbers of breakthrough new medicines

Exhibit 54: Global oncology spending by tumor US$Bn, 2019–2028



Source: IQVIA MIDAS Disease, Dec 2023; IQVIA Institute, Apr 2024.

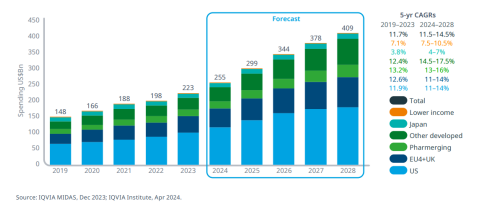
https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2024/iqvia-institute-global-oncology-trends-2024.pdf

5

Letna rast stroškov za onkološka zdravila do leta 2028

Cancer medicine spending rose to $223Bn globally in 2023 and is expected to reach $409Bn by 2028

Exhibit 51: Oncology spending by region, US$Bn

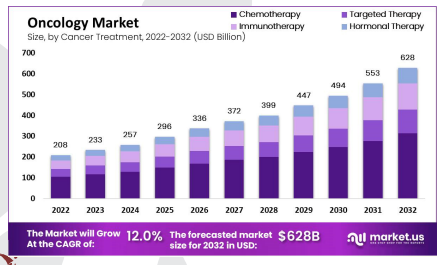


Source: IQVIA MIDAS, Dec 2023; IQVIA Institute, Apr 2024.

https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2024/iqvia-institute-global-oncology-trends-2024.pdf

6

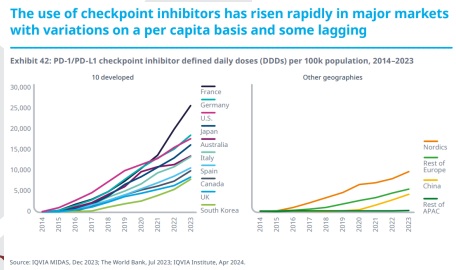
Letna rast stroškov za onkološka zdravila do leta 2032



https://market.us/report/oncology-market/

7

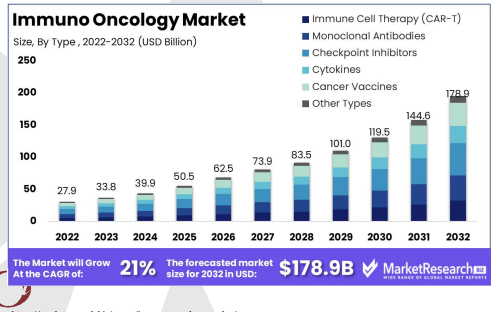
Porast stroškov za zaviralce imunskih kontrolnih točk



https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2024/iqvia-institute-global-oncology-trends-2024.pdf

8

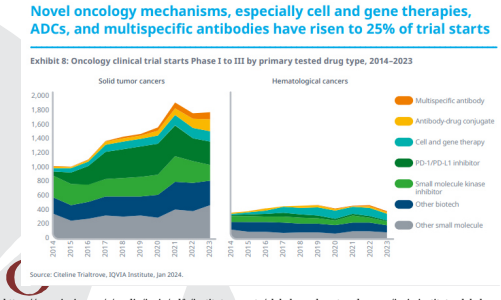
Letna rast stroškov za imunoterapijo



https://marketresearch.biz/report/immuno-oncology-market/

9

Porast stroškov za nove oblike onkoloških zdravil



https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2024/iqvia-institute-global-oncology-trends-2024.pdf

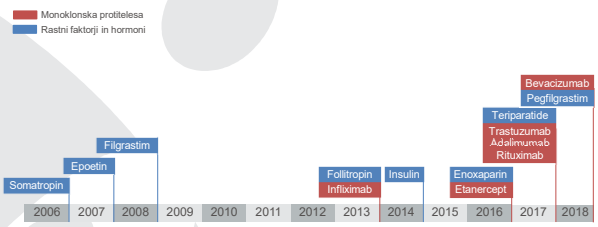
10

Biološka zdravila v onkologiji

monoklonska protitelesa, ki so usmerjena proti različnim receptorjem na rakavih celicah ali molekulam v signalnih poteh	trastuzumab, bevacizumab, rituksibab
konjugati monoklonskih protitelesi s citotoksičnimi zdravili	
konjugati monoklonskih protitelesi z radionuklidi	
zaviralci imunskih kontrolnih točk	
imunomodulatorji (interferon alfa)	
podporni dejavniki za delovanje kostnega mozga	epoetini, filgastrim, pegfilgastrim

11

Odobritve podobnih bioloških zdravil pri Evropski agenciji za zdravila (EMA)



12

Kaj omogoča uvajanje podobnih bioloških zdravil

- Dodatne terapevtske možnosti
- Širšo dostopnost učinkovitih bioloških zdravil
- Znižanje stroškov za biološka zdravila
- Prihranke v zdravstveni blagajni

13

Kaj je pomembno v klinični praksi

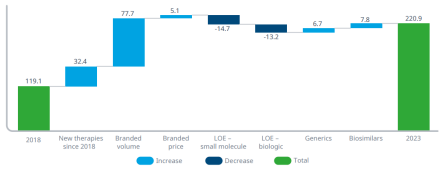
- **Odobritev s strani regulatornih agencij** (dokazana klinična učinkovitost in varnost zdravila)
- **Zasnova raziskave:** dovolj občutljiva populacija, dobro izbran cilj raziskave, podatki o preklopu
- Zdravilo **na voljo** v bolnišnični lekarni
  - *zagotovljena zaloga*
  - *na voljo vse farmacevtske oblike*
- **Zagotovljena sledljivost zdravila** (zapis z lasniškim imenom v CIPRO in vzpostavljena farmakovigilanca)
- **Čas prisotnosti proizvajalca** (proizvodni proces) na tržišču

14

Vpliv uporabe podobnihbioloških zdravil na celoten strošek za zdravila v onkologiji

Growth in oncology spending is driven by brand volume and new products offset by losses of exclusivity

Exhibit 52: Spending and growth drivers constant US$Bn, 2018–2023



Source: IQVIA MIDAS, Dec 2023.

https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2024/iqvia-institute-global-oncology-trends-2024.pdf

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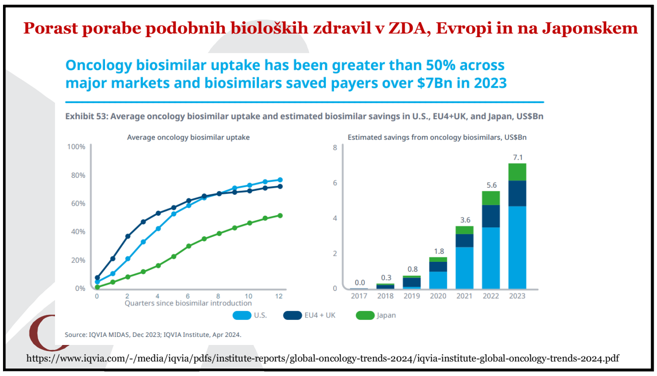
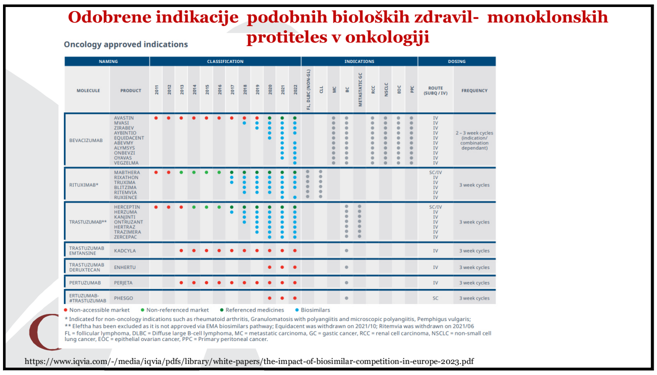
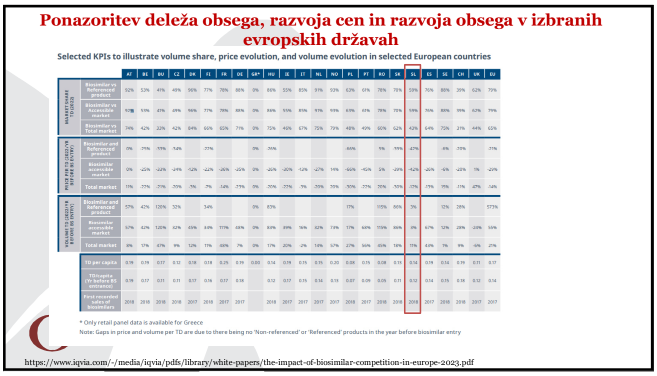

Porast porabe podobnih bioloških zdravil v ZDA, Evropi in na Japonskem
Oncology biosimilar uptake has been greater than 50% across major markets and biosimilars saved payers over $7Bn in 2023
Exhibit 53: Average oncology biosimilar uptake and estimated biosimilar savings in U.S., EU4+UK, and Japan, US$Bn
Average oncology biosimilar uptake
Quarters since biosimilar introduction
Estimated savings from oncology biosimilars, US$Bn
0.0
0.3
0.8
1.8
3.6
5.6
7.1
U.S.
EU4 + UK
Japan
Source: IQVIA MIDAS, Dec 2023; IQVIA Institute, Apr 2024.
https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncology-trends-2024/iqvia-institute-global-oncology-trends-2024.pdf

16

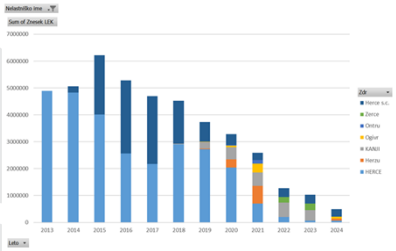

Odobrene indikacije podobnih bioloških zdravil- monoklonskih protiteles v onkologiji
Oncology approved indications
https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2023.pdf

17


Ponazoritev deleža obsega, razvoja cen in razvoja obsega v izbranih evropskih državah
Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries
https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2023.pdf

18

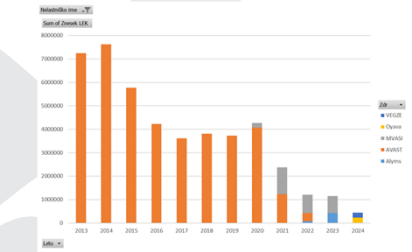
Znižanje stroškov za trastuzumab z uvajanjem biološko podobnih zdravil na OIL



Vir: podatki Lekarne OIL

19

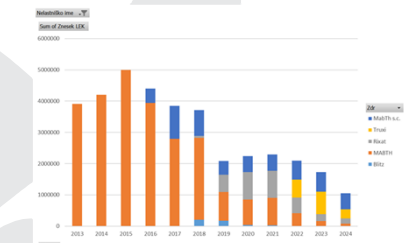
Znižanje stroškov za bevacizumab z uvajanjem bioloških podobnih zdravil na OIL



Vir: podatki Lekarne OIL

20

Znižanje stroškov za rituksinab z uvajanjem bioloških podobnih zdravil na OIL



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ZAKLJUČEK

- Podobna biološka zdravila vse bolj postajajo nepogrešljiv del zdravstvene oskrbe, saj znižujejo cene in povečujejo dostopnost zdravil.
- To še posebej velja za onkološko zdravljenje, kjer podobna biološka zdravila pomagajo razširiti dostop do oskrbe bolnikov z rakom tudi v ekonomsko manj močnih državah.

22

Podobna biološka zdravila: izkušnje s področja revmatologije

Biosimilars: Experiences in Rheumatology

Iztok Holc

Univerzitetni klinični Center Maribor, Oddelek za revmatologijo

Povzetek

Podobno biološko zdravilo (PBZ) je biološko zdravilo, za katerega je pridobljeno dovoljenje za promet po preteku patentne zaščite originalnega referenčnega zdravila. Prednosti PBZ so: nižja cena zdravil, varčevanje denarja v zdravstvu in lažja dostopnost bioloških zdravil. Izzivi na katere moramo biti pozorni so: ekstrapolacija indikacij, imunogenost in zamenljivost. Raziskave podpirajo prehod z originatorjev na PBZ, a svetujejo previdnost.

V prispevku bom predstavil rezultate prehoda iz originatorja infliksimaba na PBZ na Oddelku za revmatologijo UKC Maribor.

Abstract

A biosimilar medicine (BSM) is a biological medicine for which marketing authorization is granted after the patent protection of the original reference medicine has expired. The benefits of BSMs include lower drug prices, cost savings in the healthcare system, and better access to biological medicines. Challenges we must be aware of include extrapolation of indications, immunogenicity, and interchangeability. Research supports the transition from originators to BSMs but advises caution. In my lecture, I will present the results of the switch from the originator drug infliximab to a BSM in the Department of Rheumatology University Medical Centre Maribor.

Zamenljivost bioloških in podobnih bioloških zdravil, izkušnje z zamenjavo infliksimaba

IZTOK HOLC
ODDELEK ZA REVMATOLOGIJO
KLINIKA ZA INTERNO MEDICINO
UKC MARIBOR

1

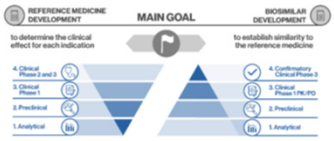
Podobno biološko zdravilo (PBZ)

Je biološko zdravilo, za katerega je pridobljeno dovoljenje za promet po preteku patentne zaščite originalnega referenčnega zdravila

NI identično (struktura protitelesa, proizvodni proces, celična linija,...).

JE primerljivo glede na izkazano učinkovitost, varnost in kakovost.

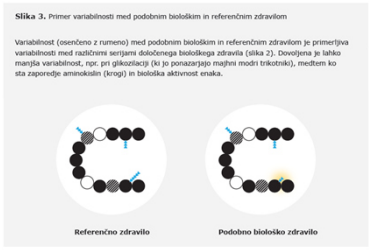
DOKAZANO s kliničnimi preskušanji in z raziskavami bioekvivalence.



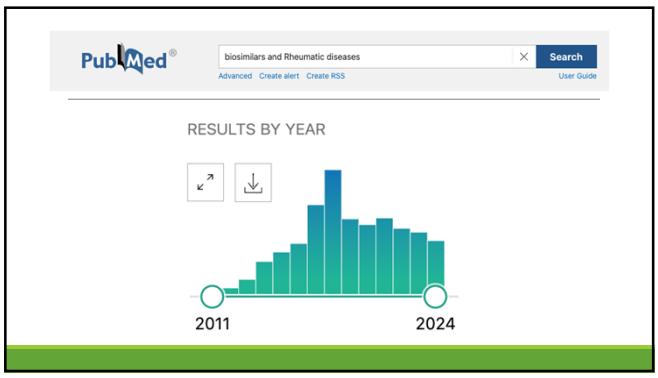
EMA je prvič sprejela smernice glede podobnih bioloških zdravil leta 2005, posodobitev leta 2014.

Vir: Sandoz Gastroenterology Biosimilar Switch Newsletter

2



3



4

Terminologija

Zamenljivost (angl. interchangibility) = praksa zamenjave enega zdravila za drugega s pričakovano enakim kliničnim rezultatom pri enaki klinični uporabi pri kateremkoli bolniku s strinjanjem predpisovalca

Substitucija = praksa zamenjave zdravila za drugo zamenljivo zdravilo na lekarniškem nivoju, brez konzultacije predpisovalca

Switching = odločitev lečečega zdravnika o zamenjavi zdravila za drugo zdravilo z enakim terapevtskim ciljem pri zdravljenem bolniku; tudi zamenjava originalnega biološkega zdravila s PBZ

- **Cross-switching** = zamenjava enega PBZ z drugim PBZ oz. navzkrižna zamenjava
- **Reverse-switching** = zamenjava PBZ z originalnim biološkim zdravilom oz. povratna zamenjava
- **Multiple-switching** = večkratna zamenjava

5

PBZ za zdravljenje vnetnih revmatskih bolezni

INFLIKSIMAB (REMICADE ®)

2013 Remsima® (Celltrion/Oktal Pharma)
Inflectra® (Pfizer)
~~Flixabi® (Samsung Bioepis/Biogen)~~
Zessly® (Sandoz/Lek)

ETANERCEPT (ENBREL ®)

Benepali ® (Samsung)
Erelzi ® (Sandoz)

ADALIMUMAB (HUMIRA ®)

2018 Amgevita® (Amgen)
Imraldi® (Samsung Bioepis/Biogen)
~~Hulio® (FujiFilm/Viatris)~~
Hyrimoz® (Sandoz/Lek)
Idacio® (Fresenius Kabi/Mediasi)
Hukyndra® (Stada)
Yuflyma® (Celltrion/Oktal Pharma)

RITUXIMAB (MABTHERA ®)

Rixathon ® (Sandoz/Lek)
Truxima ® (Celtrion)
Blitzima ® (Celtrion)

TOCILIZUMAB (ROACTEMRA ®)

Tyenne ® (Fresenius Kabi)
Tofidence ® (Bioggen Netherlands)

Navedena so vsa zdravila z lastniškimi imeni, ki so dostopna na Centralna baza zdravil 2 - iskanje (cbz.si)

6

Prednosti PBZ

1. **Nižja cena zdravil**
   - V EU cca. 30% (do 69% na Norveškem);
   - razlika napram generičnim zdravilom, kjer je cena nižja za 70-80%
2. **Varčevanje denarja v zdravstvu**
   - Znižanje stroškov za raziskave in razvoj zdravil
   - Konkurenca
   - Enostavnejša pot odobritve zdravila
   - Skupaj v EU in ZDA bi lahko v 5 letih privarčevali od 56-112 milijard $
3. **Lažja dostopnost bioloških zdravil**
   - Več bolnikov zdravljenih z biološkim zdravilom (na Češkem leta 2014 zdravljenih 1000 bolnikov več kot leta 2013)
   - Bolniki lahko biološko zdravilo dobijo prej v poteku svoje bolezni
   - Več izbire med biološkimi zdravili

7

Izzivi PBZ

1. **Ekstrapolacija indikacij**
   - Klinične raziskave pri RA in axSpA, tudi pri KVČB
   - Specifična distribucija v tkivih, različna učinkovitost v različnih tkivih
   - Razlike v ADCC = antibody-dependent cell-mediated cytotoxicity
   - Razlike v populacijah bolnikov (starost, pridružene bolezni, druga zdravila,...)
   - Razlike v odmerkih, načinu aplikacije
2. **Imunogenost**
   - Nepredvidljivo tveganje za imunogenost zaradi razlik med molekulami
   - Pojav protiteles proti zdravilu – alergije, izguba učinka
   - Vplivi: proizvodnja, post-translacijske modifikacije, pot aplikacije, značilnosti bolnika,...
3. **Zamenljivost**
   - Switching; že dokazi o varnosti iz kliničnih observacijskih raziskav
   - Cross-switching; že objave o zamenjavi med PBZ
   - Reverse-switching; že objave o menjavi s PBZ na originalni IFX
   - Multiple-switching; že objave o do 3x zamenjavah

Podatki se nanašajo na raziskave na naslednjih straneh.

8

Podatki o zamenljivosti

ENKRATNA ZAMENJAVA

RCT :
- NOR-SWITCH (IFX za KVČB)
- REFLECTIONS (IFX za RA)
- ADMYRA (ADA za RA)

Podatki iz klinične prakse
- IFX in ADA
- Pri KVČB in revmatoloških vnetnih boleznih

VEČKRATNA ZAMENJAVA (DO 3X)

Podatki iz klinične prakse
- Originalni IFX– PBZ 1. – PBZ 2.
- PBZ 1. – PBZ 2.
- IFX in ADA
- Pri KVČB in revmatoloških vnetnih boleznih

Sistematični pregled raziskav

RCT (randomized controlled trial), IFX (infliksimab), ADA (adalimumab)

9

NOR-SWITCH raziskava


THE LANCET

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

Jørgensen KK, Olsen IC, Goll GL, et al. Lancet 2017; 389: 2304-16

Randomizirana prospektivna raziskava (Norveška)

- 1x zamenjava z originalnega IFX na PBZ
- 482 bolnikov (KVČB, RA, PsA, Ps)
- 52 tednov opazovanja

Zdravljenje s CT-P13 je primerljivo glede učinkovitosti in prenašanja.

Rezultati podpirajo prehod z IFX na CT- P13 iz ne-medicinskih razlogov.

Priporočajo previdnost pri posploševanju na druga biološka zdravila.

Potrebne nadaljnje študije za preučitev povratnih in navzkrižnih zamenjav med IFX in PBZ.

10

Clinical Gastroenterology and Hepatology 2019;17:2506–2513

Outcomes of Patients With Inflammatory Bowel Diseases Switched From Maintenance Therapy With a Biosimilar to Remicade

Akos Ilias,[1,2] Kata Szanto,[1,2] Lorant Gonczi,[1] Zsuzsanna Kurti,[1] Petra Anna Golovics,[3] Klaudia Farkas,[3] Eszter Schafer,[3] Zoltan Szepes,[3] Balazs Szalay,[3] Aron Vincze,[3] Tamas Szamosi,[3] Tamas Molnar,[3] and Peter Laszlo Lakatos[1,4]

Prospektivna observacijska raziskava (Madžarska)

- Zamenjava PBZ z originalnim IFX
- 174 bolnikov s KVČB, 78% s CB; 8% imelo 2x zamenjavo (IFX-PBZ-IFX)
- 24 tednov opazovanja

Niso zaznali sprememb v vzdrževanju remisije, TL, pojavu protiteles proti IFX

Ni bilo novih varnostnih signalov.

TL = through level

11

Raziskave z večkratnimi zamenjavami

ORIGINAL ARTICLE
uegjournal WILEY

Multiple infliximab biosimilar switches appear to be safe and effective in a real-world inflammatory bowel disease cohort

Beatriz Gros[1,2] | Nikolas Plevris[1] | Nathan Constantine-Cooke[3,4] | Mathew Lyons[1] | Claire O'Hare[1,2] | Colin Noble[1] | Ian D. Arnott[1] | Gareth-Rhys Jones[5,6] | Charlie W. Lees[5,6] | Lauranne A. A. P. Derikx[1,7,8]

Prospektivna kohortna raziskava enega centra (Edinburg, ZK)

- 297 bolnikov, 66% CB
- do 3x zamenjava (67 bolnikov)
- 24 tednov opazovanja (max 8 mesecev)
- Številne zamenjave so učinkovite in varne

Prospektivna multicentrična kohortna raziskava (Nizozemska)

- 176 bolnikov, 71% CB
- 2x zamenjava (69 bolnikov)
- 12 mesecev opazovanja
- Večkratne zamenjave so učinkovite in varne

CROHN'S & COLITIS FOUNDATION

Multiple Switches From the Originator Infliximab to Biosimilars Is Effective and Safe in Inflammatory Bowel Disease: A Prospective Multicenter Cohort Study

Jurij Hanzel, MD,[1,2] Jeroen M. Jansen, MD,[3] Rinze W. F. ter Steege, MD, PhD,[3] Krisztina B. Gecse, MD, PhD,[4] and Geert R. D'Haens, MD, PhD[4]

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Sistematična analiza

BioDrugs (2022) 36:625–637
https://doi.org/10.1007/s40259-022-00546-6
SYSTEMATIC REVIEW

Switching from One Biosimilar to Another Biosimilar of the Same Reference Biologic: A Systematic Review of Studies

Hillel P. Cohen[1] · Sohaib Hachaichi[2] · Wolfram Bodenmueller[3] · Tore K. Kvien[4] · Silvio Danese[5] · Andrew Blauvelt[6]

- Zamenjave med PBZ (IFX, ADA, ETA, RTX)
- 3657 bolnikov (KVČB, RA, PsA, SpA,...)
- Vse raziskave so bile opazovalne narave; RCT
- Študije so bile heterogene glede na velikosti, zasnovo in končne cilje.

Ni bilo zaznati zmanjšanja učinkovitosti ali povečanja neželenih učinkov po zamenjavi med PBZ

IFX = infliksimab, ADA = adalimumab, ETA = etanercept, RTX = rituksimab

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Skupna izjava EMA-HMA o medsebojni zamenljivosti bioloških zdravil (september 2022)

Podobna biološka zdravila, odobrena v EU, so medsebojno zamenljiva.

Zamenljivost se nanaša na možnost zamenjave enega zdravila za drugo zdravilo, ki naj bi imelo enak klinični učinek.

HMA in EMA menita, *da je podoben biološki izdelek, ko je odobren v EU, medsebojno zamenljiv, kar pomeni, da se lahko uporablja namesto referenčnega izdelka (ali obratno) ali pa se en podoben biološki izdelek nadomesti z drugim podobnim biološkim izdelkom istega referenčnega izdelka.* Zamenjava se lahko izvede le po skrbni preučitvi odobrenih pogojev uporabe (tj. po posvetovanju z najnovejšimi informacijami o zdravilu).

Odločitve o tem, kako izvajati *medsebojno zamenljivost z zamenjavo* (pod nadzorom predpisovalca) *in/ali nadomestitvijo* (praksa izdaje enega zdravila namesto drugega zdravila brez posvetovanja z predpisovalcem, kot je samodejna zamenjava na ravni lekarne), niso v pristojnosti agencije EMA in jih *upravljajo posamezne države članice*.

14

Nocebo učinek

Bolnikova negativna pričakovanja ob zamenjavi za PBZ lahko vodijo v neuspešnost zdravljenja.

Nocebo učinek je moč zmanjšati z **individualno prilagojenim izobraževanjem bolnikov**, pri čemer je odnos med bolnikom in njegovimi zdravstvenimi delavci priznan kot ključni dejavnik za sprejemanje podobnih bioloških zdravil.

NOCE-BIO konsenzusna skupina je priporočila multidisciplinarna prizadevanja za zmanjšanje učinka nocebo pri bolnikih s KVČB, ki se zdravijo s PBZ,z ukrepi za zdravnike, medicinske sestre, psihologe in farmacevte.

Edukacija!

15

Journal of the Canadian Association of Gastroenterology, 2020, 3(5), 228–233
doi: 10.1093/jcag/gwz043
Original Article
Advance Access publication 3 January 2020

Original Article

The Law and Ethics of Switching from Biologic to Biosimilar in Canada

Blake Murdoch, JD, MBA[1], Timothy Caulfield, LLM, FRSC, FCAHS
Health Law Institute, Faculty of Law, University of Alberta, Edmonton, Alberta, Canada
Correspondence: Timothy Caulfield, Health Law Institute, Faculty of Law, University of Alberta, Edmonton, Alberta T6G 2H5, Canada, e-mail: caulfield@ualberta.ca

„Čeprav v Kanadi ni neodtujljive pravice do financiranja referenčnih bioloških zdravil, lahko imajo zdravniki v nekaterih okoliščinah kot zastopniki bolnikov pravno obveznost, da se v imenu bolnikov zavzemajo za to, da le-ti ostanejo na referenčnem biološkem zdravilu."

„Zaradi polemik v zvezi z zamenjavo (za PBZ) bo vsaj del postopka soglasja zahteval robustno in temeljito razkritje ustreznih tveganj, koristi in razumnih razlogov za zamenjavo."

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Zamenjava v UKC Maribor

REMICADE - ZESSLY

17

Remicade®-Zessly® v UKC Maribor 2023

31 bolnikov (20M, 11Ž)

	Povprečje	Min	Max
Starost ob dg (L)	39,3	14,6	63,04
Starost 2024 (L)	56.85	24.04	77.34
Starost ob th z biol. (L)	45,09	19,71	68,28
Starost ob začetku Zessly-a (L)	55.94	23.05	78.24

18

Diagnoze

RA	3
PsA	2
AS	21
SpA	3
JRA	1
Entero-SpA	1

19

Trajanje zdravljenja

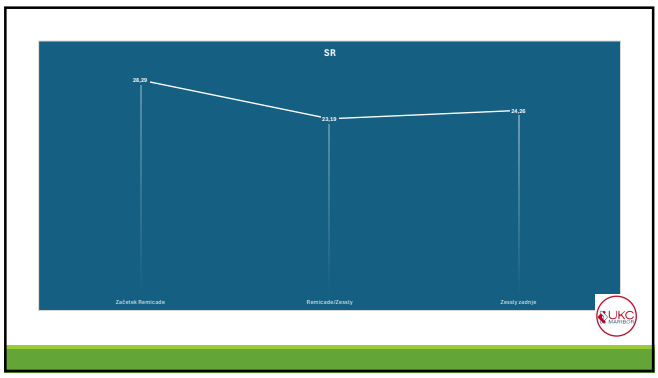
	Povprečje (m)	Min (m)	Max (m)
Trajanje zdravljenja Remicade®	127.8	8,93	197.17
Trajanje zdravljenja Zessly®	11.13	7.9	12.6

20

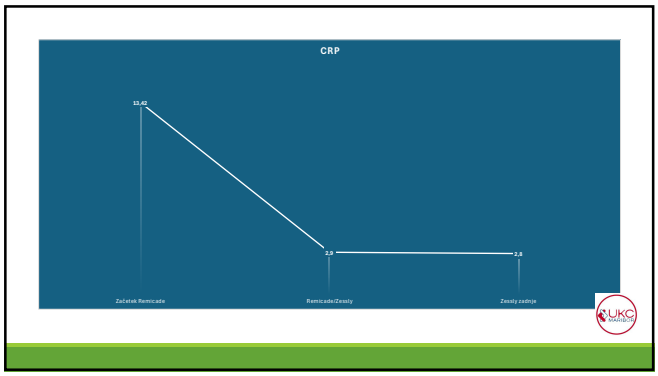
Zdravljenje pred infliximabom

- 1 bolnica – etanercept
- 1 bolnik - adalimumab in etanercept
- 1bolnica - adalimumab
- 1 bolnik - etanercept in adalimumab

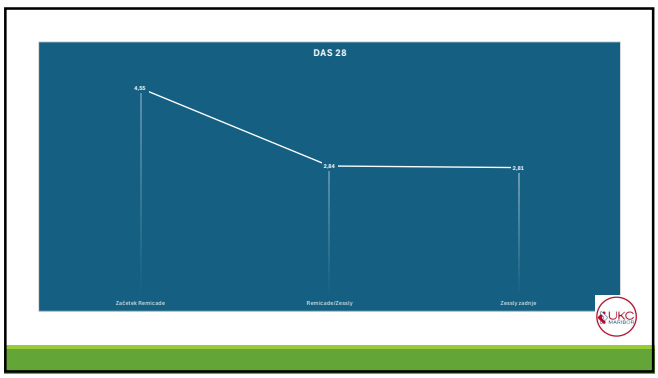
21


SR
28,20
23,19
24,26
Začetek Remicade
Remicade/Zessly
Zessly zadnje

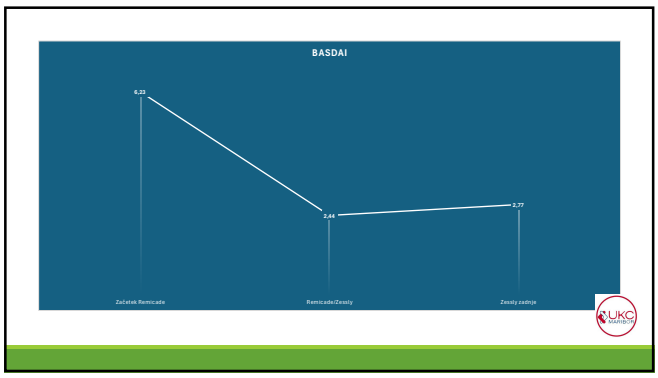
22


CRP
13,42
2,9
2,8
Začetek Remicade
Remicade/Zessly
Zessly zadnje

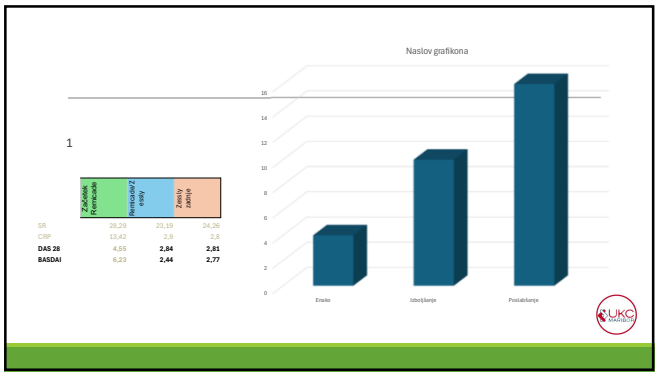
23


DAS 28
4,55
2,64
2,61
Začetek Remicade
Remicade/Zessly
Zessly zadnje

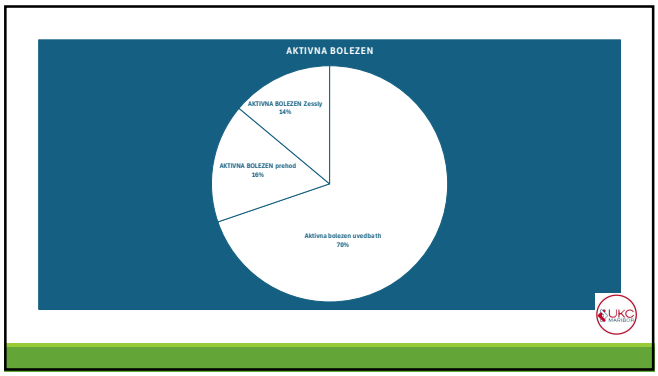
24


BASDAI
6,23
2,44
2,77
Začetek Remicade
Remicade/Zessly
Zessly zadnje

25


Naslov grafikona
1
Začetek Remicade
Remicade/Zessly
Zessly zadnje
SR 28,29 23,19 24,26
CRP 13,42 2,9 2,8
DAS 28 4,55 2,84 2,81
BASDAI 6,23 2,44 2,77
Enako
Izboljšanje
Poslabšanje

26


AKTIVNA BOLEZEN
AKTIVNA BOLEZEN Zessly 14%
AKTIVNA BOLEZEN prehod 16%
Aktivna bolezen uvedbath 70%

27

Prekinitev terapije z Zessly-jem

- Neučinkovitost – 2 bolnici
- Prehod na RTX zaradi pljučne prizadetosti

28

Neželeni učinki

- pri Zeslly-ju nismo opazovali neželenih učinkov

29

Zaključek

- Od odobritve prvega podobnega biološkega zdravila v EU je v > 15 letih že > 400 milijonov bolnikovih let izkušenj.
- Pomembno je skrbno (post-marketinško) sledenje učinkovitosti in varnosti.
- Edukacija uporabnikov je potrebna.
- Nepristransko obveščanje o koristih in ev. izzivih podobnih bioloških zdravil.
- Podatki o imunogenosti v luči različnih oblik zamenjevanja oz. „switching-a".
- Potreben je konsenz zainteresiranih deležnikov (bolniki, medicinsko osebje, plačnik, politika…)
- **V naši kohorti so PBZ enako učinkovita in varna kot originator**.

30

Hvala!

31

5 pravil za uspešno uvedbo podobnih bioloških zdravil

The 5 rules for successful introduction of biosimilars

Arnold G. Vulto

Erasmus University Medical Center, Dept. Of Hospital Pharmacy, Rotterdam, The Netherlands

Povzetek

Za uspešno uvedbo biološko podobnega zdravila ni ene same rešitve. Obstaja veliko spremenljivk, kot so nacionalni zdravstveni sistem, pravila o povračilih, status zavarovanja, odnos zdravnikov, zaupanje pacientov, kulturne razlike itd. Naše raziskave na tem področju so pokazale pet skupnih dejavnikov pri uspešnih uvedbah biološko podobnih zdravil:

- Pristop več deležnikov: v proces odločanja in izvedbe uvedbe biološko podobnega zdravila v bolnišnico vključite vse deležnike v zdravstvenem sistemu (predpisovalce, medicinske sestre, vodstvo, farmacevte itd.).
- Komunicirajte s principom enotnega glasu (vsi, ki so vključeni v proces uvajanja podobnega biološkega zdravila, sporočajo enako) za preprečitev lažnih nocebo učinkov.
- Obvestite pacienta, da se bo zdravljenje začelo/nadaljevalo z enako varno in učinkovito alternativo.
- Zdravstvene delavce nagradite za njihov čas in trud, ki ga vložijo v uvedbo spremembe, z neko obliko finančnega nadomestila.
- Transparentno poročajte, kaj se bo zgodilo s prihranki in kako bodo uporabljeni/ponovno vloženi v zdravstveni sistem.

Če so biološko podobna zdravila v določenih primerih manj uspešna, je običajno eden ali več teh dejavnikov odsoten ali slabo izveden.

Na Nizozemskem so bila ta načela vključena v t. i. Orodjarno za biološko podobna zdravila – uradno podprto s strani Združenja nizozemskih bolnišničnih farmacevtov in Federacije vseh združenj medicinskih specialistov. Orodjarna med drugim vključuje diagram poteka, odločitvena drevesa in vzorčna pisma. Ta močan kolegialen pristop je omogočil, da so se v bolnišnicah pri delu izognili mnogim razpravam in se je izkazal za zelo učinkovit pri sprejemanju biološko podobnih zdravil.

Referenca:
https://gbiomed.kuleuven.be/english/research/50000715/52577001/mabel/Keyinsights

Abstract

There is no single solution for a successful introduction of a biosimilar. There are many variables, like the national health system, reimbursement rules, insurance status, physicians'

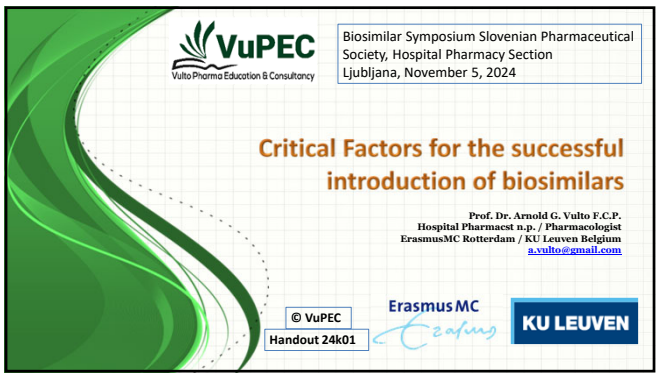
attitude, patients trust, cultural differences etc. Our research in this area has indicated 5 common denominators in successful biosimilar adoptions:

Multistakeholder approach: involve everybody (prescribers, nurses, management, pharmacists etc.) in the health system in the decision and execution process of launching a biosimilar in a hospital.

- Communicate with a one-voice principle to avoid false nocebo-effects.
- Inform the patient that the treatment will be initiated / continued with an equally safe and effective alternative.
- Compensate the healthcare professionals (HCPs) for their time and effort to make the change possible with a form of gain sharing.
- Report transparently what will happen with the savings and how they will be used / reinvested in the healthcare system.
- If biosimilars are less succesful in certain situations, usually one or more of these factors are absent or where badly implemented.

In The Netherlands these principles were included in a Biosimilar Toolbox – officially endorsed by the Dutch Hospital Pharmacists Association and the Federation of all Medical Specialist Associations. It includes amongst others a flow diagram, decision trees and example letters. This powerful collegial approach has avoided a lot of discussion on the workfloor in the hospital and appeared very powerful in the acceptance of biosimilars.

Reference:
https://gbiomed.kuleuven.be/english/research/50000715/52577001/mabel/Keyinsights


VuPEC
Vulto Pharma Education & Consultancy
Biosimilar Symposium Slovenian Pharmaceutical Society, Hospital Pharmacy Section
Ljubljana, November 5, 2024
Critical Factors for the successful introduction of biosimilars
Prof. Dr. Arnold G. Vulto F.C.P.
Hospital Pharmacst n.p. / Pharmacologist
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a.vulto@gmail.com
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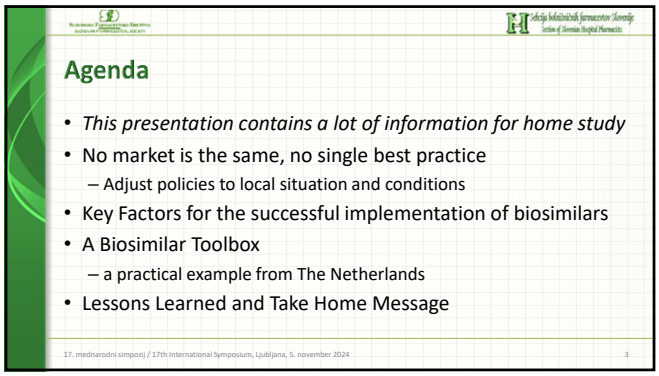
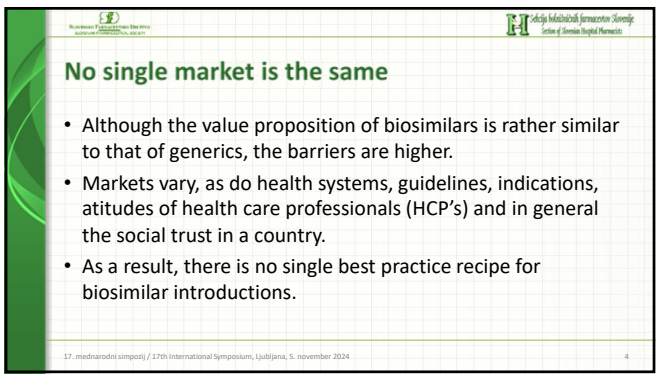
Erasmus MC
KU LEUVEN


Agenda
• This presentation contains a lot of information for home study
• No market is the same, no single best practice
– Adjust policies to local situation and conditions
• Key Factors for the successful implementation of biosimilars
• A Biosimilar Toolbox
– a practical example from The Netherlands
• Lessons Learned and Take Home Message
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
3


No single market is the same
• Although the value proposition of biosimilars is rather similar to that of generics, the barriers are higher.
• Markets vary, as do health systems, guidelines, indications, atitudes of health care professionals (HCP's) and in general the social trust in a country.
• As a result, there is no single best practice recipe for biosimilar introductions.
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
4

Not all biosimilar markets are equal: Three archetypes of maturity phase and their characteristics in Europe

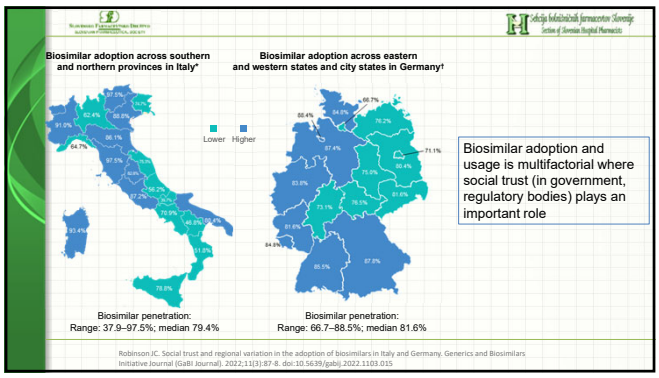
	PRIMARY OPPORTUNITIES	MAIN BIOSIMILAR BENEFIT
INVEST No or little access to reference biologics because of their high cost	Offer the first opportunity for treatment with biologics	Lower-cost biosimilars allow markets to provide access to biologics that were previously too costly
EXPAND Some access to reference biologics, but some patients/subpopulations do not qualify for reimbursement or have only limited access	Expand access to biologics to a greater number of patients	Cost savings from biosimilars allow expanded access to biologic therapies, treating more patients
HARVEST Access to biologics is high and covers reference biologics and biosimilars	Appropriately recycle cost savings Sustain biosimilar competition	Competition of manufacturers for stable, lower-cost supply of biologics while driving innovation

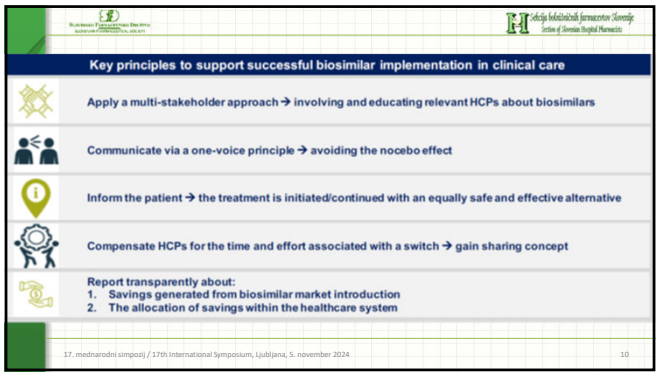
- Mestre-Ferrandiz J et al. Expert Rev Pharmacoecon Outcomes Res 2024; 24:237–250.
- Available at: https://www.tandfonline.com/doi/full/10.1080/14737167.2023.2297926;

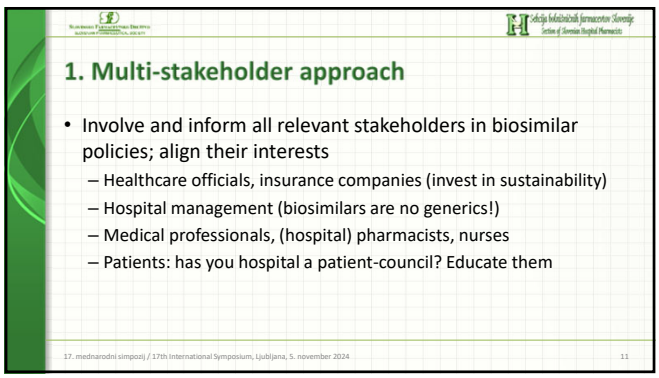
- Mestre-Ferrandiz J et al. Expert Rev Pharmacoecon Outcomes Res 2024; 24:509-519.
- Available at: https://www.tandfonline.com/doi/full/10.1080/14737167.2024.2310684.

Example of different indications

- A failing treatment for a reumatoid arthritis patient has different consequences than for an colitis ulcerosa patient.
- In RA there are many follow-up treatments, for UC it could mean quite dramatic surgery.
- That's why we see more hesitation among gastro-enterologists who have little knowledge about biosimilars.


Biosimilar adoption across southern and northern provinces in Italy*
Biosimilar adoption across eastern and western states and city states in Germany†
Lower
Higher
Biosimilar adoption and usage is multifactorial where social trust (in government, regulatory bodies) plays an important role
Biosimilar penetration:
Range: 37.9–97.5%; median 79.4%
Biosimilar penetration:
Range: 66.7–88.5%; median 81.6%
Robinson JC. Social trust and regional variation in the adoption of biosimilars in Italy and Germany. Generics and Biosimilars Initiative Journal (GaBI Journal). 2022;11(3):87-8. doi:10.5639/gabij.2022.1103.015


Key principles to support successful biosimilar implementation in clinical care
Apply a multi-stakeholder approach → involving and educating relevant HCPs about biosimilars
Communicate via a one-voice principle → avoiding the nocebo effect
Inform the patient → the treatment is initiated/continued with an equally safe and effective alternative
Compensate HCPs for the time and effort associated with a switch → gain sharing concept
Report transparently about:
1. Savings generated from biosimilar market introduction
2. The allocation of savings within the healthcare system
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
10


1. Multi-stakeholder approach
• Involve and inform all relevant stakeholders in biosimilar policies; align their interests
– Healthcare officials, insurance companies (invest in sustainability)
– Hospital management (biosimilars are no generics!)
– Medical professionals, (hospital) pharmacists, nurses
– Patients: has you hospital a patient-council? Educate them
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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2. Apply the one-voice principle

- Avoid the nocebo-effect

Pharmaceutical Medicine
https://doi.org/10.1007/s40290-024-00541-y

SYSTEMATIC REVIEW

Mitigating the Nocebo Effect in Biosimilar Use and Switching: A Systematic Review

Elif Car[1] · Yannick Vandenplas[1] · Teresa Barcina Lacosta[1] · Steven Simoens[1] · Isabelle Huys[1] · Arnold G. Vulto[1,2] · Liese Barbier[1]

Accepted: 26 September 2024
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In Press
October 2024

Are you familiar with the nocebo-effect?

- The nocebo effect (in Latin "I shall harm") is defined as the occurrence of negative expectations about a treatment or a change in treatment which can lead to worsened symptoms (i.e., lower treatment efficacy) or adverse events (AEs) and cannot be attributed to the pharmacologic action of a treatment itself
- The nocebo effect is highly relevant to use of biosimilars including switching from originator to biosimilars due to misconceptions and lack of confidence among health care providers and patients about biosimilars

3. Inform the patient properly

- Treatment will be continued (or initiated) with a different brand with equal efficacy and safety
- Keep a positive tone: this is good for all of us
- Taylor information to the attitude and level of understanding of a patient
- Avoid random searching the internet
- Keep it "small"

4. Compensate professionals

- HCP's invest a lot of time and effort to make this happen
- Appreciate those efforts and reward them
  - Design gain sharing schemes with your management

BioDrugs
https://doi.org/10.1007/s40259-022-00523-z

ORIGINAL RESEARCH ARTICLE

Qualitative Analysis of the Design and Implementation of Benefit-Sharing Programs for Biologics Across Europe

Teresa Barcina Lacosta[1] · Arnold G. Vulto[1,2] · Adina Turcu-Stiolica[3] · Isabelle Huys[1] · Steven Simoens[1]

Accepted: 22 February 2022
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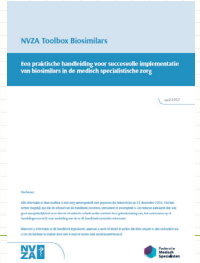
5. Report benefits transparently

- What has been achieved?
  - Like: cost reduction, more patients treated, new services, more staff
- Where have the savings gone?
  - Reinvested in healthcare, benefitting patients?

Biosimilar Toolbox: A practical example from The Netherlands

- Introduction of biosimilars follows the rules of "change management": inform and partner with everybody involved
- Engage with your medical specialist associations
  - Align your objectives and team up together
  - This avoids needless discussions on the hospital floor
- Together we have built a "biosimilar toolbox"

Dutch Hospital Pharmacists Association and Dutch Federation of Medical Specialists



- **Toolbox biosimilars (2017)**
- A practical guide for succesful implementation
  - Scientific background, definitions and position papers (e.g. MEB)
  - New patients, existing patients
  - Implementation: task force and roadmap
  - Policies for transitioning
  - Information materials, letters

MEB, Medicines Evaluation Board

Lessons learned:
Communication, communication and communication

- Multistakeholder approach
  - Involve all those relevant: prescribers, pharmacists, patients, nurses, procurement department and hospital managers
  - Shared decision making
- Speak with one voice
  - Avoid distorting information
  - Beware of attribution and nocebo-effects
- Make selection process transparent for all
  - Advantages and disadvantages
  - Who will gain (preferably: gain sharing)

Take-home message

- Implementation of a biosimilar policy should be managed as a project
  - Multidisciplinary, One Voice, Shared decision making, Gain sharing
  - Specialised nurses involved in educating patients
  - Engage a patient representative in your biosimilar policy
  - Organise disease-specific patient information sessions on biosimilars
  - Run as pharmacy special biosimilar sessions with all relevant medical departments
- The Dutch NVZA / Federation Medical Specialists Toolbox based on “best practice”
- Procurement is a three-party process:
  - Medical stakeholder, Specialist pharmaceuticals, Procurement/contract specialist

Be transparent, educate and communicate, communicate, communicate
Hospital pharmacists play an essential tole in acceptanc and implementation of biosimilars.
Take your responsibility!

Izkušnje bolnišničnega farmacevta z implementacijo podobnih bioloških zdravil v klinični praksi

The experience of a hospital pharmacist with the implementation of biosimilars in clinical practice

Tomislav Laptoš

Univerzitetni klinični center Ljubljana, Lekarna

Povzetek

Uvedba podobnih bioloških zdravil v klinično prakso je prinesla v bolnišnično okolje precejšnje spremembe. V prvi fazi je bilo na strani (predvsem predpisovalcev) zaznati določeno nezaupanje zaradi kompleksne sestave molekul, zahtevnejše analitike proizvajalca in potencialne imunogenosti.

Poleg tega je spremenjena cenovna politika in po eni strani tako večja razpoložljivost tako podobnih kot referenčnih bioloških zdravila vplivala na obseg dela v bolnišničnih lekarnah. Ker so se hkrati z uvajanjem in kliničnimi izkušnjami širile tako indikacije kot rahljale omejitve predpisovanja s strani ZZZS, je bilo opazno znatno povečanje števila bolnikov, ki se (predvsem kronično) zdravilo bolnišnično oz. v okviru enodnevnih obravnav.

Aplikacija (podobnih) bioloških zdravil je primarno intravenska ali subkutana. Pot aplikacije, tveganje za mikrobiološko kontaminacijo pri pripravi, cena in možnost racionalne uporabe zdravila so dejavniki, ki narekujejo centralizirano pripravo omenjenih zdravil. Farmacevti v bolnišničnih lekarnah smo bili tako postavljeni pred izziv, kako vsem bolnikom, ki ta zdravila prejemajo, omogočiti, da prejmejo farmacevtski pripravek, ki bo izdelan v skladu s sodobnimi standardi, bo na voljo v za bolnika ustreznem odmerku in v razumnem času, predvsem v okviru enodnevne bolnišnične obravnave.

Uvedba podobnih bioloških zdravil je izpostavila vlogo in osvetlila celosten vpogled bolnišničnega farmacevta na celoten postopek uporabe zdravila, od postopka preskrbe in svetovanja ob uporabi v bolnišničnem okolju do racionalizacije in optimizacije priprave in aplikacije zdravila oziroma farmacevtskega pripravka.

Abstract

The introduction of biosimilar drugs into clinical practice has led to significant changes in the hospital environment. In the early stages, there was a noticeable lack of confidence among prescribers due to the complex composition of the molecules, the more sophisticated analytics required by manufacturers and the potential for immunogenicity.

In addition, changing pricing policies and the increased availability of both biosimilars and reference biological drugs have affected the workload in hospital pharmacies. With the expansion of indications and the easing of prescribing restrictions by our health insurance

institute, as well as the clinical experience gained, the number of patients receiving (mainly chronic) treatments in hospitals or as part of same-day procedures increased significantly.

The administration of (biosimilar) biological drugs is mainly intravenous or subcutaneous. The route of administration, the risk of microbiological contamination during preparation, the cost and the potential for rational use of the drug are factors that make centralized preparation of these drugs necessary. Thus, pharmacists in hospital pharmacies are faced with the challenge of ensuring that all patients receiving these drugs receive a pharmaceutical preparation that is prepared to modern standards, in a dosage appropriate to the patient and within a reasonable time, particularly in the context of same-day hospital care.

The introduction of biosimilars has highlighted the role and comprehensive insight of hospital pharmacists in the entire drug utilization process, from procurement procedures and hospital consultation to streamlining and optimizing drug preparation and administration.


Izkušnje bolnišničnega farmacevta z implementacijo podobnih bioloških zdravil v klinični praksi
Tomislav Laptoš, mag. farm., spec.
Univerzitetni klinični center Ljubljana
Lekarna

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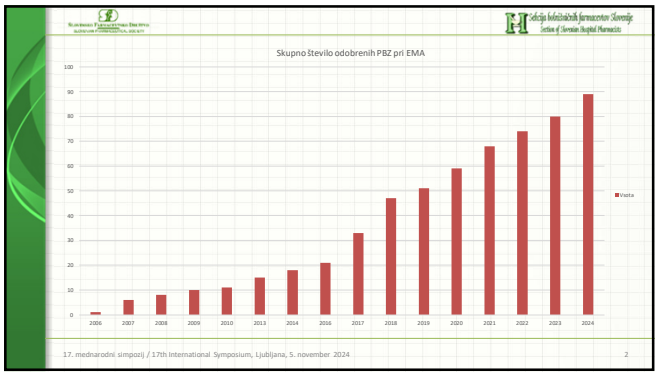
Skupno število odobrenih PBZ pri EMA
2006
2007
2008
2009
2010
2013
2014
2016
2017
2018
2019
2020
2021
2022
2023
2024
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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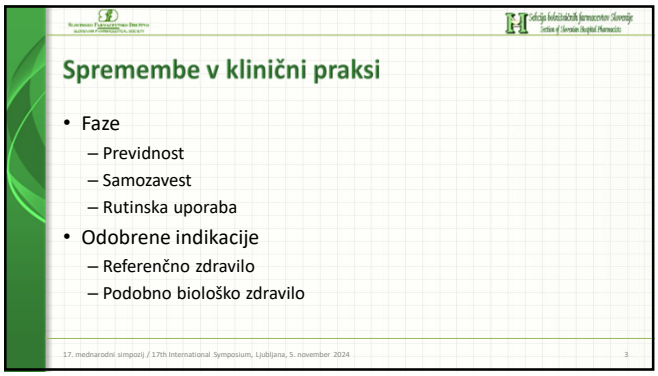
Spremembe v klinični praksi
• Faze
– Previdnost
– Samozavest
– Rutinska uporaba
• Odobrene indikacije
– Referenčno zdravilo
– Podobno biološko zdravilo
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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3

Finančni vidik

- ZZZS
  - Vzdržnost javnih financ
  - Ohranjanje obsega „košarice“
  - Širjenje naroba bolnikov
- Javni razpisi
  - Izbira enega ponudnika
  - Izbira več ponudnikov
  - Tveganje pri stabilnosti preskrbe

4

Bolnikov vidik

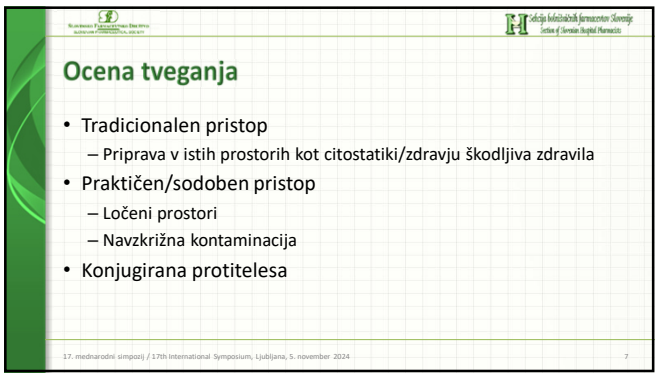
- Hospitalna uporaba
  - Manj izrazita časovna komponenta
  - Kompleksnejši bolniki
- Ambulantna uporaba
  - Časovna komponenta
  - Manj kompleksni bolniki

5

Priprava farmacevtskih pripravkov

- Breckenridgevo poročilo (1976)
  - Letter: Addition of drugs to intravenous fluids
- Dejavniki tveganja
  - Pot aplikacije
  - Mikrobiološka kontaminacija
  - Cena/racionalna uporaba

6


Ocena tveganja
• Tradicionalen pristop
– Priprava v istih prostorih kot citostatiki/zdravju škodljiva zdravila
• Praktičen/sodoben pristop
– Ločeni prostori
– Navzkrižna kontaminacija
• Konjugirana protitelesa
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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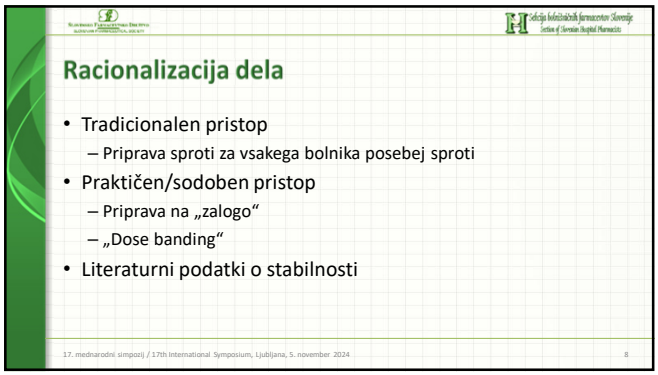
Racionalizacija dela
• Tradicionalen pristop
– Priprava sproti za vsakega bolnika posebej sproti
• Praktičen/sodoben pristop
– Priprava na „zalogo“
– „Dose banding“
• Literaturni podatki o stabilnosti
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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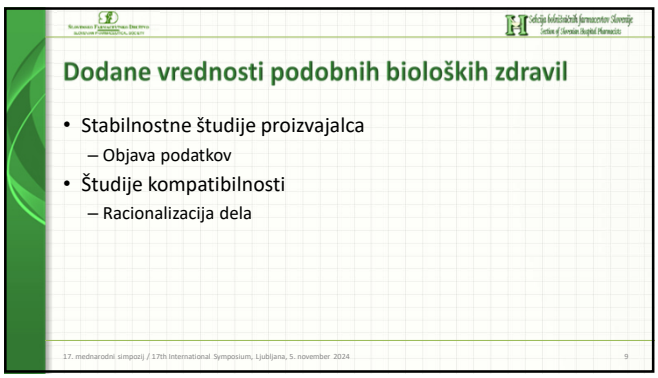
Dodane vrednosti podobnih bioloških zdravil
• Stabilnostne študije proizvajalca
– Objava podatkov
• Študije kompatibilnosti
– Racionalizacija dela
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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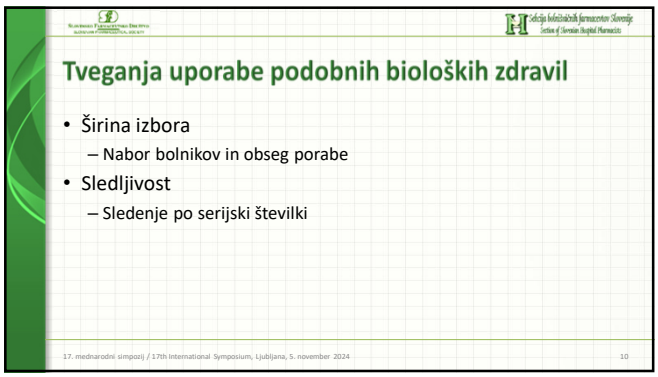
Tveganja uporabe podobnih bioloških zdravil
• Širina izbora
– Nabor bolnikov in obseg porabe
• Sledljivost
– Sledenje po serijski številki
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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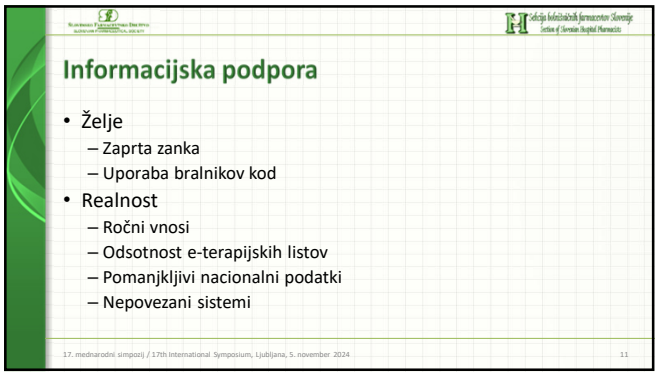
Informacijska podpora
• Želje
– Zaprta zanka
– Uporaba bralnikov kod
• Realnost
– Ročni vnosi
– Odsotnost e-terapijskih listov
– Pomanjkljivi nacionalni podatki
– Nepovezani sistemi
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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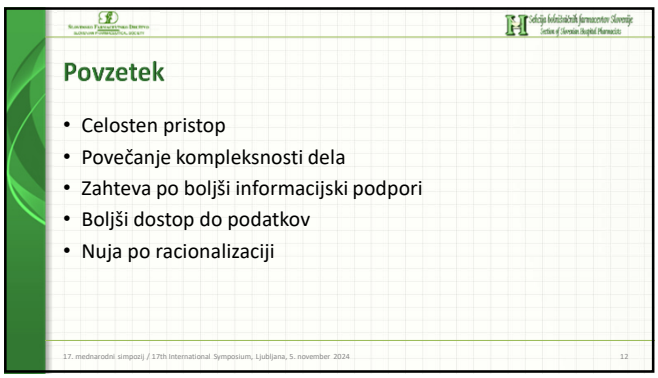
Povzetek
• Celosten pristop
• Povečanje kompleksnosti dela
• Zahteva po boljši informacijski podpori
• Boljši dostop do podatkov
• Nuja po racionalizaciji
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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Vloga medicinske sestre pri implementaciji podobnih bioloških zdravil

The role of the nurse in the implementation of biosimilars

Boštjan Jovan

Univerzitetni klinični center Ljubljana, Klinični oddelek za hematologijo

Povzetek

Medicinske sestre igrajo ključno vlogo pri uspešni implementaciji PBZ, saj se soočajo s skepticizmom bolnikov, pomanjkanjem informacij in pomanjkljivim izobraževanjem. Njihovo znanje, izkušnje in sposobnosti pri izobraževanju bolnikov so nepogrešljive pri zagotavljanju varnosti in učinkovitosti zdravljenja. Zdravstvene institucije morajo zagotoviti ustrezno usposabljanje in podporo za medicinske sestre, da bodo lahko učinkovito izvajale svoje naloge. Poleg tega se morajo nenehno izobraževati o novih produktih, saj je razvoj novih produktov in njihov prihod na trg zelo velik.

Prve informacije o zdravljenju bolniku poda zdravnik, medicinske sestre so pogosto tiste, ki bolnikom nudijo podrobne informacije o zdravljenju, kar lahko vključuje razlago mehanizma delovanja PBZ, njihovih koristih in potencialnih neželenih učinkih, saj bolniki v bolnišnicah farmacenta praviloma niti ne vidijo. MS pridobijo bolnikovo soglasje, uvedejo vensko kanilo, po kateri bo zdravilo aplicirano, aplicirajo premedikacijo, PBZ, in skrbijo za opazovanje njegovega zdravstvenega stanja in pravočasne ukrepe ob nastanku neželenih reakcij. Za razliko od zdravnikov in farmacevtov MS velikokrat izpadejo iz procesa izobraževanja, saj slovenska zakonodaja omogoča informiranje predpisovalcev in farmacevtov o zdravilih in omejuje izobraževanje medicinskih sester. Izobražena medicinska sestra je ključna že pri pridobitvi soglasja (ustnega ali pisnega) za aplikacijo zdravila, za kar potrebuje visok nivo znanja tako o zdravilu, kot njegovih neželenih učinkih. Neželene učinke mora najprej prepoznati in nato na njih pravilno ukrepati. V kolikor bo bolnik utrpel katerega od neželenih učinkov in bodo ukrepi premišljeni in suvereni se bo bolnik počutil varno kljub nastalim težavam in bo pomirjen ob nadaljevanju zdravljanja. V nasprotnem primeru se lahko bolnik ustraši in ne želi nadaljevati s predvidenim zdravljenjem, kar ima lahko usodne posledice za njegovo zdravje.

Vloga MS pri implementaciji PBZ je zelo pomembna in le dobro educirana MS bo lahko podala relevantne informacije bolniku, primerno skrbela za njegovo zdravstveno stanje, zdravljenje glede na bolnikove potrebe individualno prilagodila ter v sodelovanju z ostalim multidisciplinarnim timom bolnikom omogočila optimalno zdravljenje.

Abstract

Nurses play a crucial role in the successful introduction of biosimilars (BSM) as they are confronted with patient skepticism, lack of information and insufficient training. Their knowledge, experience and patient education skills are critical to the safety and efficacy of the

treatment. Healthcare facilities must provide adequate training and support to nurses so that they can perform their duties effectively. In addition, nurses need to be constantly informed about new products, as the development of new products and their market launch are of great importance.

The first information about the treatment is given to the patient by the doctor, but it is often the nurses who provide detailed information about the treatment, e.g. the mechanism of action of BSM, its benefits and possible side effects, as patients do not usually visit pharmacists in the hospital. The nurse obtains the patient's consent, connects the intravenous cannula through which the drug is administered, administers the premedication and BSM, monitors the patient's health status and takes timely action in case of side effects.

Unlike doctors and pharmacists, nurses often fall outside the training process, as Slovenian legislation allows prescribers and pharmacists to be trained in medicines, but restricts the training of nurses. A well-trained nurse is crucial when it comes to obtaining consent (verbal or written) to administer medication, which requires a high level of knowledge about both the drug and its possible side effects. They must first recognize adverse effects and then respond appropriately. If a patient experiences adverse effects, careful and confident action on the part of the nurse will help the patient to feel safe despite the problems that arise and to continue treatment with peace of mind. If, on the other hand, the patient feels frightened and hesitates to continue the prescribed treatment, this can have serious consequences for their health.

The role of nurses in the implementation of BSM is very important. Only well-trained nurses are able to provide patients with relevant information, take appropriate care of their health condition, individualize treatment to the patient's needs and work with the multidisciplinary team to provide optimal treatment for patients.


Vloga medicinske sestre pri implementaciji PBZ
Sklop: Praktični vidiki in kako premagati ovire
Boštjan Jovan, dipl. zn.

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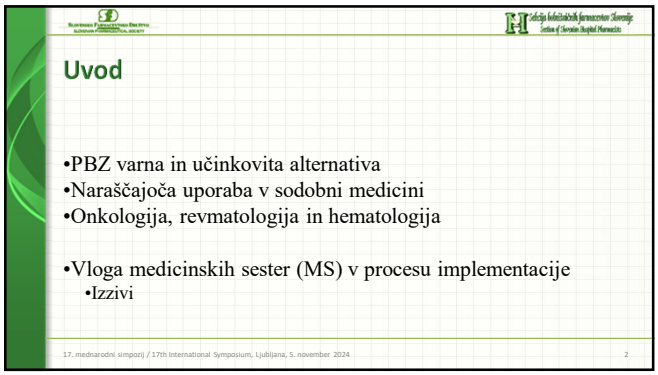
Uvod
•PBZ varna in učinkovita alternativa
•Naraščajoča uporaba v sodobni medicini
•Onkologija, revmatologija in hematologija
•Vloga medicinskih sester (MS) v procesu implementacije
•Izzivi
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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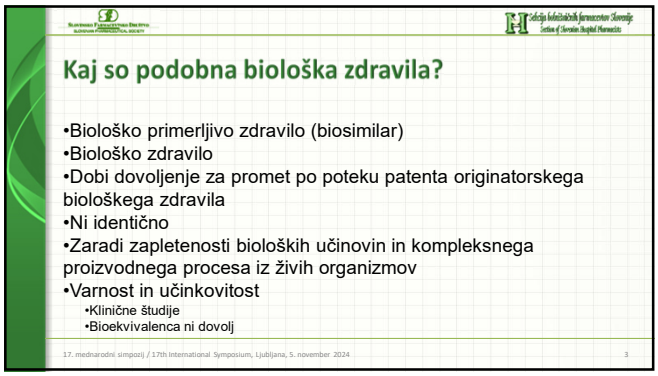
Kaj so podobna biološka zdravila?
•Biološko primerljivo zdravilo (biosimilar)
•Biološko zdravilo
•Dobi dovoljenje za promet po poteku patenta originatorskega biološkega zdravila
•Ni identično
•Zaradi zapletenosti bioloških učinovin in kompleksnega proizvodnega procesa iz živih organizmov
•Varnost in učinkovitost
•Klinične študije
•Bioekvivalenca ni dovolj
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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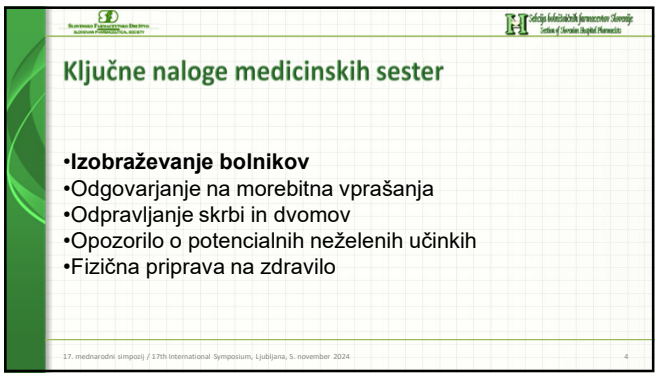
Ključne naloge medicinskih sester
•Izobraževanje bolnikov
•Odgovarjanje na morebitna vprašanja
•Odpravljanje skrbi in dvomov
•Opozorilo o potencialnih neželenih učinkih
•Fizična priprava na zdravilo
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
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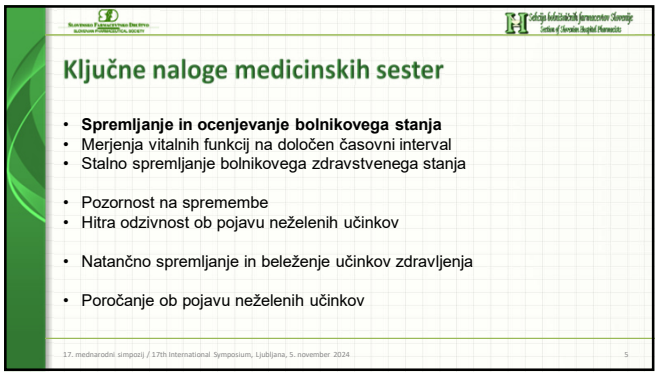
Ključne naloge medicinskih sester
• Spremljanje in ocenjevanje bolnikovega stanja
• Merjenja vitalnih funkcij na določen časovni interval
• Stalno spremljanje bolnikovega zdravstvenega stanja
• Pozornost na spremembe
• Hitra odzivnost ob pojavu neželenih učinkov
• Natančno spremljanje in beleženje učinkov zdravljenja
• Poročanje ob pojavu neželenih učinkov
17. mednarodni simpozij / 17th International Symposium, Ljubljana, 5. november 2024
5

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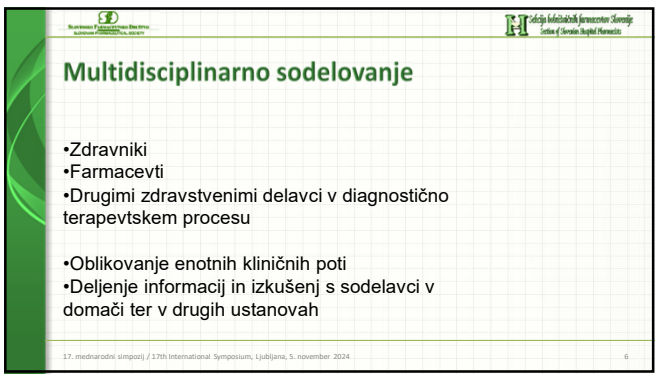
Multidisciplinarno sodelovanje
•Zdravniki
•Farmacevti
•Drugimi zdravstvenimi delavci v diagnostično terapevtskem procesu
•Oblikovanje enotnih kliničnih poti
•Deljenje informacij in izkušenj s sodelavci v domači ter v drugih ustanovah
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6

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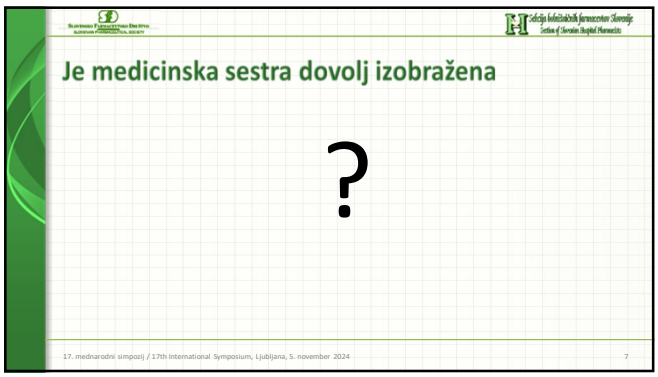
Je medicinska sestra dovolj izobražena
?
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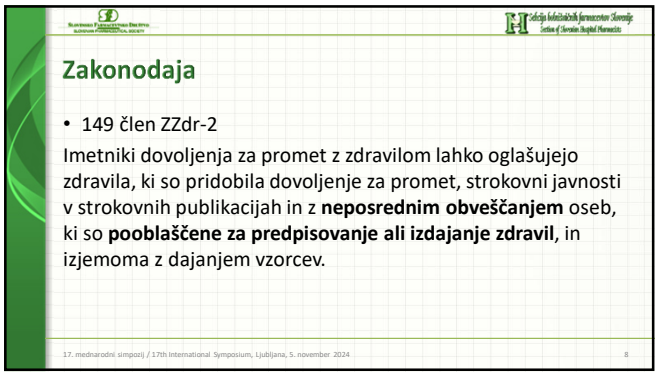
Zakonodaja
• 149 člen ZZdr-2
Imetniki dovoljenja za promet z zdravilom lahko oglašujejo zdravila, ki so pridobila dovoljenje za promet, strokovni javnosti v strokovnih publikacijah in z **neposrednim obveščanjem** oseb, ki so **pooblaščene za predpisovanje ali izdajanje zdravil**, in izjemoma z dajanjem vzorcev.
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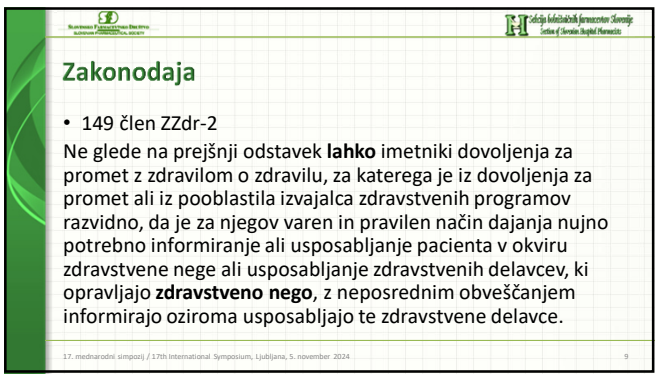
8

8


Zakonodaja
• 149 člen ZZdr-2
Ne glede na prejšnji odstavek **lahko** imetniki dovoljenja za promet z zdravilom o zdravilu, za katerega je iz dovoljenja za promet ali iz pooblastila izvajalca zdravstvenih programov razvidno, da je za njegov varen in pravilen način dajanja nujno potrebno informiranje ali usposabljanje pacienta v okviru zdravstvene nege ali usposabljanje zdravstvenih delavcev, ki opravljajo **zdravstveno nego**, z neposrednim obveščanjem informirajo oziroma usposabljajo te zdravstvene delavce.
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9

9

Zakonodaja

- 149 člen ZZdr-2
- Imetnik dovoljenja za promet z zdravilom mora voditi seznam strokovnih sodelavcev, ki:
- Oglašujejo zdravila
- So pooblaščene za predpisovanje in izdajanje zdravil

- Kje so MS???

10

Zakonodaja

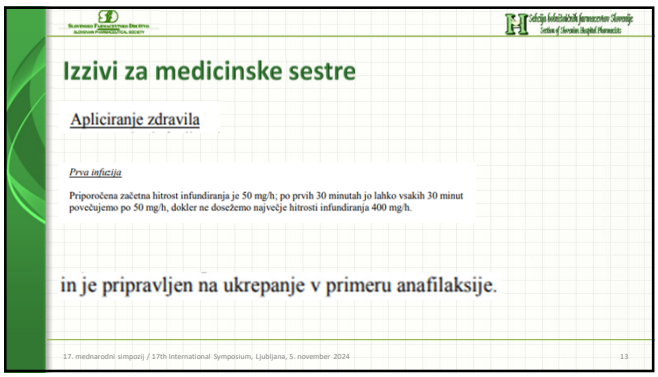
- 149 člen ZZdr-2
- Imetniki dovoljenja za promet z zdravilom, proizvajalci zdravil, poslovni subjekti, ki nastopajo v imenu proizvajalcev in tistih, ki opravljajo promet z zdravili, ter podružnice tujih proizvajalcev zdravil **lahko** omogočajo osebam, ki **predpisujejo** in **izdajajo zdravila** ter **osebam iz drugega odstavka** tega člena pridobivanje dodatnih znanj o novih zdravilih na znanstvenih in strokovnih srečanjih, vendar le v skladu z omejitvami iz šestega in sedmega odstavka tega člena.

11

Priprava zdravil farmacevt / MS

- Vrsta in količina topila
- Volumen nosilne tekočine
- Posebnosti pri pripravi
- Stabilnost po rekonstituciji
- Tveganja za lastno zdravje
  - Priprava
  - Aplikacija
  - Delo z bolnikom

12


Izzivi za medicinske sestre
Apliciranje zdravila
Prva infuzija
Priporočena začetna hitrost infundiranja je 50 mg/h; po prvih 30 minutah jo lahko vsakih 30 minut povečujemo po 50 mg/h, dokler ne dosežemo največje hitrosti infundiranja 400 mg/h.
in je pripravljen na ukrepanje v primeru anafilaksije.
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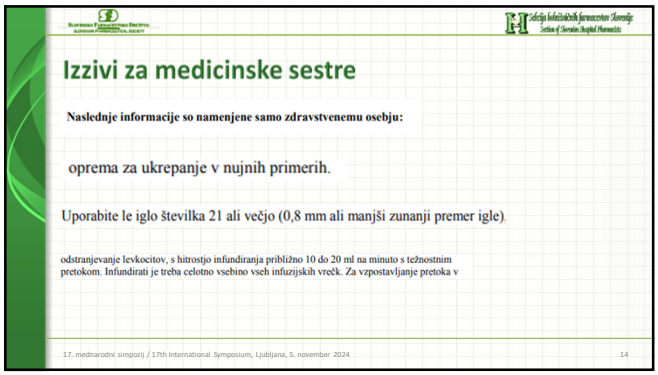
13


Izzivi za medicinske sestre
Naslednje informacije so namenjene samo zdravstvenemu osebju:
oprema za ukrepanje v nujnih primerih.
Uporabite le iglo številka 21 ali večjo (0,8 mm ali manjši zunanji premer igle).
odstranjevanje levkocitov, s hitrostjo infundiranja približno 10 do 20 ml na minuto s težnostnim pretokom. Infundirati je treba celotno vsebino vseh infuzijskih vrečk. Za vzpostavljanje pretoka v
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Izzivi za medicinske sestre
Osnovni podatki
Indikacije
Odmerjanje
Kontraindikacije
Posebna opozorila
Interakcije
Nosečnost
Sposobnost vožnje
Neželeni učinki
Preveliko odmerjanje
Farmakodinamika
Farmakokinetika
https://mediately.co/si/drugs
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15

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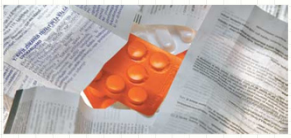
Izzivi za medicinske sestre

- Navodila za uporabo



https://medicina.bhc.si/aktualno/obetajo-se-spremembe-navodil-za-uporabo-zdravil/a/278640

16

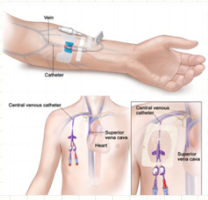
Izzivi za medicinske sestre

- Čas potreben od aplikacije premedikacije do zdravila?
- Spremljanje vitalnih funkcij?
  - Katere?
  - Kako pogosto/stalni monitoring?
  - Koliko časa po zaključku?
- So neželeni učinki enaki kot pri originatorju?

17

Izzivi za medicinske sestre

https://e-katalog.lkpp.go.id/katalog/produk/detail/82122600



https://www.kmedhealth.com/iv-line/

18

Priporočila za prakso

•Spodbujati timsko delo in multidisciplinarno komunikacijo
•Razviti izobraževalne programe za medicinske sestre
• Omogočiti dostop do evropskih/svetovnih smernic
• V navodila dodati za MS pomembne podatke
•Poudariti klinično pomembne razlike z originatorjem

19

Zaključek

•Pomembna vloga medicinskih sester pri uspešni implementaciji PBZ
•Razviti izobraževalne programe za medicinske sestre
•Velika količina PBZ

•Prispevek k varnosti in učinkovitosti zdravljenja

20

Viri

- Beck, K. L., et al. (2019). "The role of nurses in the management of biosimilars." *Nursing Management*, 50(4), 36-42.
- Cohen, H., et al. (2018). "Patient understanding of biosimilars: the role of nursing education." *Journal of Nursing Practice*, 18(2), 105-111.
- García-Alonso, C., et al. (2021). "Monitoring biosimilar therapy: A nursing perspective." *Clinical Nursing Studies*, 9(3), 45-52.
- Hawkes, J. S., et al. (2018). "Multidisciplinary collaboration in biosimilar implementation." *Biosimilars Journal*, 7(1), 17-24.
- Kirk, R. M., et al. (2020). "Ethical considerations in the use of biosimilars." *Nursing Ethics*, 27(2), 430-439.
- Schneider, C. K., et al. (2017). "Biosimilars: what nurses need to know." *Journal of Nursing*, 34(5), 43-49.
- JAZMP
- Navodila za uporabo različnih proizvajalcev

21


Hvala
I STAB PEOPLE
For a Living
Podobno ≠ enako ☺
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Ali bomo v prihodnosti imeli na voljo podobna biološka zdravila?

Will we have biosimilars in the future? The biosimilar Void

Aurelio Arias

IQVIA

Povzetek

Čeprav je konkurenca biološko podobnih zdravil v Evropi igrala ključno vlogo pri doseganju znatnih prihrankov v zdravstvu in širšem dostopu pacientov do ključnih zdravil, spreminjajoča se narava prihodnjih iztekov patentne zaščite pomeni, da konkurenca in s tem povezani prihranki niso vedno zagotovljeni.

V tem prispevku predstavljamo aktualno analizo dejavnikov, ki vplivajo na spreminjajočo se raven aktivnosti na področju bioloških zdravil v Evropi, s poudarkom na razredih bioloških zdravil, pri katerih obstaja tveganje za zelo omejeno uvedbo biološko podobnih zdravil. Gre za koncept, imenovan "praznina biološko podobnih zdravil."

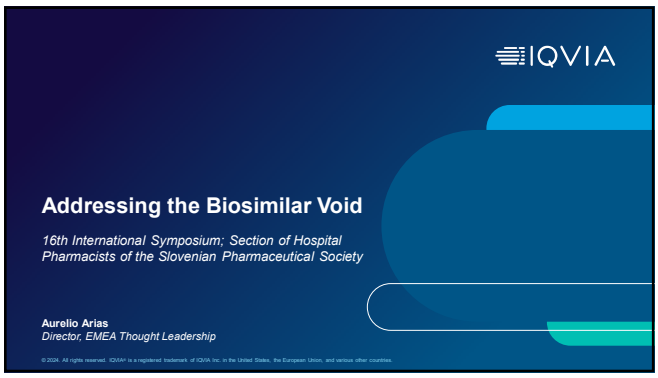
To bi lahko imelo širok spekter negativnih posledic za prihodnjo komercialno privlačnost sektorja biološko podobnih zdravil, prihranke za zdravstveni sistem in dostop pacientov do zdravil.

Abstract

While biosimilar competition in Europe has played a vital role in achieving significant healthcare savings and expanding patient access to key medicines, the changing nature of future loss of exclusivity (LoE) events means that competition, and by extension savings, is not always guaranteed.

In this session, we provide a timely analysis of the factors underlying the changing level of biologic pipeline activity in Europe, highlighting classes of biologics that are at risk of having very little biosimilar launches for them, a concept called "the biosimilar void."

This could have wide ranging negative implications on the future commercial attractiveness of the biosimilar sector, savings for the healthcare system and access to medicines for patients.


IQVIA
Addressing the Biosimilar Void
16th International Symposium; Section of Hospital Pharmacists of the Slovenian Pharmaceutical Society
Aurelio Arias
Director, EMEA Thought Leadership
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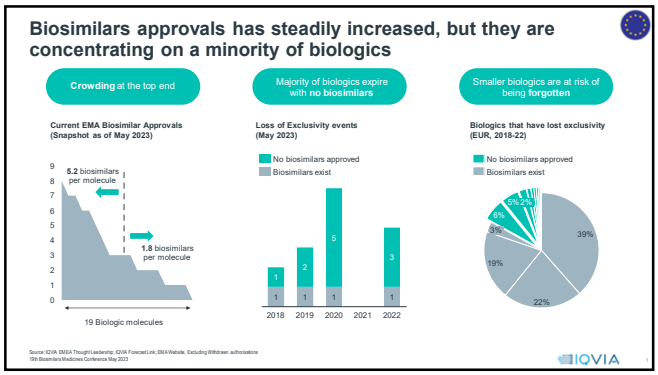
Biosimilars approvals has steadily increased, but they are concentrating on a minority of biologics
Crowding at the top end
Majority of biologics expire with no biosimilars
Smaller biologics are at risk of being forgotten
Current EMA Biosimilar Approvals (Snapshot as of May 2023)
5.2 biosimilars per molecule
1.8 biosimilars per molecule
19 Biologic molecules
Loss of Exclusivity events (May 2023)
No biosimilars approved
Biosimilars exist
2018 2019 2020 2021 2022
Biologics that have lost exclusivity (EUR, 2018-22)
No biosimilars approved
Biosimilars exist
39%
22%
19%
6%
5%
3%
2%
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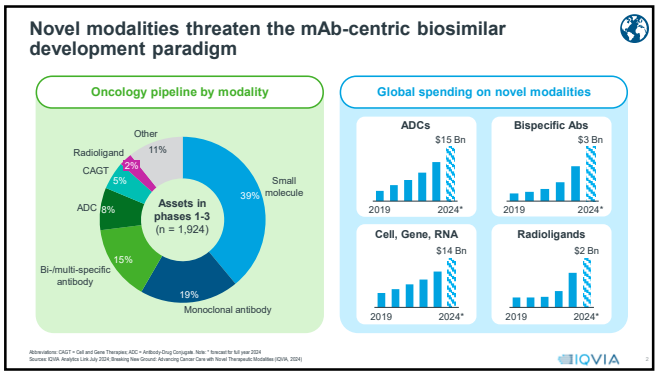
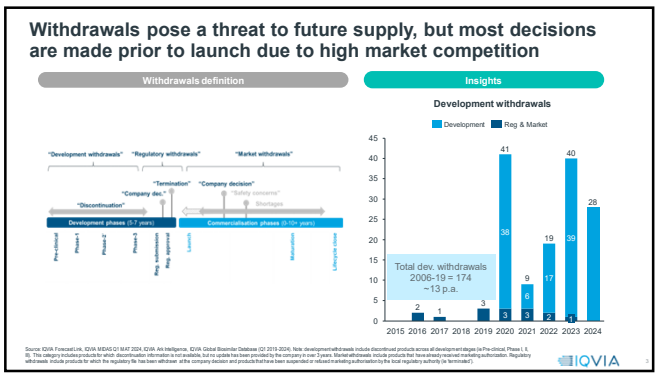
1


Novel modalities threaten the mAb-centric biosimilar development paradigm
Oncology pipeline by modality
Assets in phases 1-3 (n = 1,924)
Small molecule 39%
Monoclonal antibody 19%
Bi-/multi-specific antibody 15%
ADC 8%
CAGT 5%
Radioligand 2%
Other 11%
Global spending on novel modalities
ADCs
$15 Bn
Bispecific Abs
$3 Bn
Cell, Gene, RNA
$14 Bn
Radioligands
$2 Bn
2019
2024*
IQVIA

2


Withdrawals pose a threat to future supply, but most decisions are made prior to launch due to high market competition
Withdrawals definition
Insights
"Development withdrawals"
"Regulatory withdrawals"
"Market withdrawals"
"Termination"
"Company decision"
"Company dec."
"Discontinuation"
"Safety concerns"
Shortages
Development phases (5-7 years)
Commercialisation phases (3-10+ years)
Pre-clinical
Phase I
Phase II
Phase III
Reg. submission
Reg. approval
Launch
Maturation
Lifecycle close
Development withdrawals
Development
Reg & Market
Total dev. withdrawals 2006-19 = 174 ~13 p.a.
2015 2016 2017 2018 2019 2020 2021 2022 2023 2024
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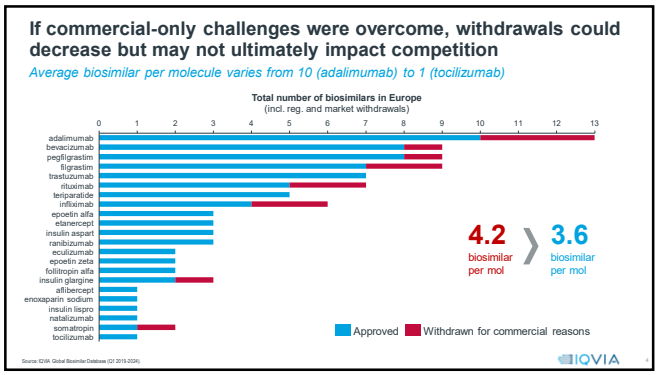
3


If commercial-only challenges were overcome, withdrawals could decrease but may not ultimately impact competition
Average biosimilar per molecule varies from 10 (adalimumab) to 1 (tocilizumab)
Total number of biosimilars in Europe
(incl. reg. and market withdrawals)
adalimumab
bevacizumab
pegfilgrastim
filgrastim
trastuzumab
rituximab
teriparatide
infliximab
epoetin alfa
etanercept
insulin aspart
ranibizumab
eculizumab
epoetin zeta
follitropin alfa
insulin glargine
aflibercept
enoxaparin sodium
insulin lispro
natalizumab
somatropin
tocilizumab
4.2 biosimilar per mol
3.6 biosimilar per mol
Approved
Withdrawn for commercial reasons
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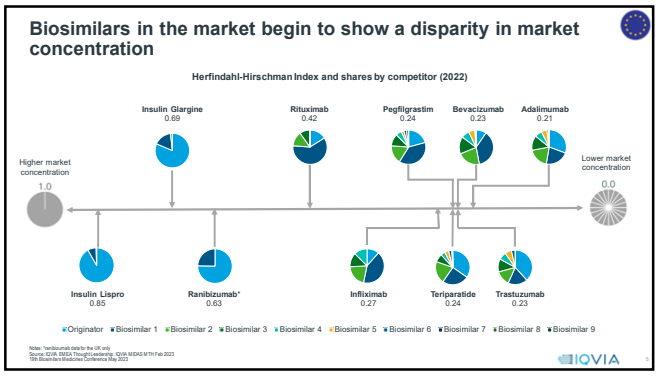
4


Biosimilars in the market begin to show a disparity in market concentration
Herfindahl-Hirschman Index and shares by competitor (2022)
Insulin Glargine 0.69
Rituximab 0.42
Pegfilgrastim 0.24
Bevacizumab 0.23
Adalimumab 0.21
Higher market concentration
1.0
Lower market concentration
0.0
Insulin Lispro 0.85
Ranibizumab* 0.63
Infliximab 0.27
Teriparatide 0.24
Trastuzumab 0.23
Originator
Biosimilar 1
Biosimilar 2
Biosimilar 3
Biosimilar 4
Biosimilar 5
Biosimilar 6
Biosimilar 7
Biosimilar 8
Biosimilar 9
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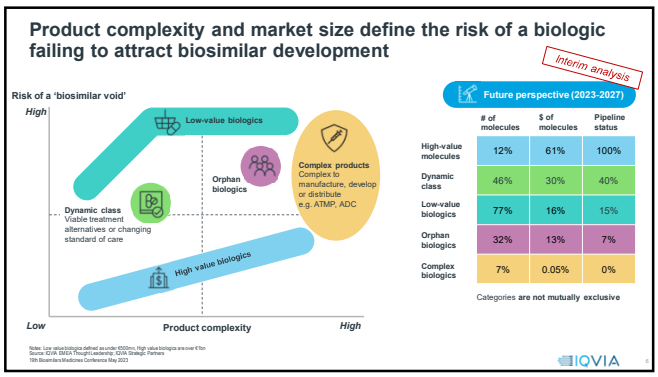
5


Product complexity and market size define the risk of a biologic failing to attract biosimilar development
Interim analysis
Risk of a 'biosimilar void'
High
Low-value biologics
Orphan biologics
Complex products
Complex to manufacture, develop or distribute e.g. ATMP, ADC
Dynamic class
Viable treatment alternatives or changing standard of care
High value biologics
Low
Product complexity
High
Future perspective (2023-2027)
# of molecules
$ of molecules
Pipeline status
High-value molecules 12% 61% 100%
Dynamic class 46% 30% 40%
Low-value biologics 77% 16% 15%
Orphan biologics 32% 13% 7%
Complex biologics 7% 0.05% 0%
Categories are not mutually exclusive
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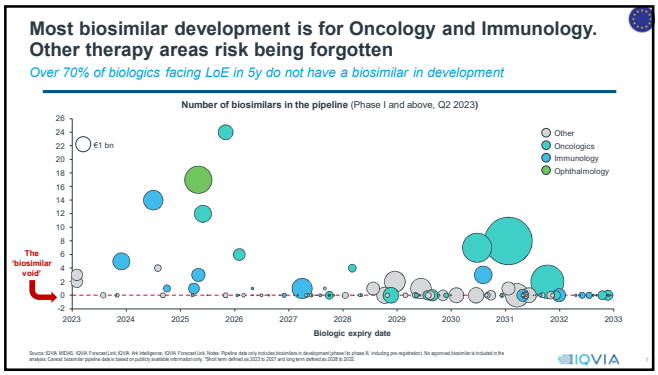
6


Most biosimilar development is for Oncology and Immunology. Other therapy areas risk being forgotten
Over 70% of biologics facing LoE in 5y do not have a biosimilar in development
Number of biosimilars in the pipeline (Phase I and above, Q2 2023)
€1 bn
Other
Oncologics
Immunology
Ophthalmology
The 'biosimilar void'
Biologic expiry date
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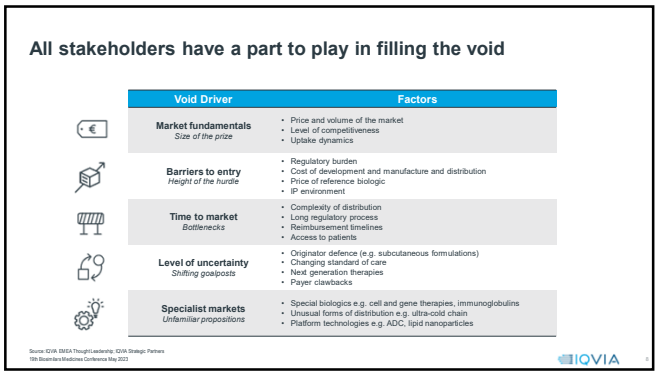
7


All stakeholders have a part to play in filling the void
Void Driver
Factors
Market fundamentals
Size of the prize
Price and volume of the market
Level of competitiveness
Uptake dynamics
Barriers to entry
Height of the hurdle
Regulatory burden
Cost of development and manufacture and distribution
Price of reference biologic
IP environment
Time to market
Bottlenecks
Complexity of distribution
Long regulatory process
Reimbursement timelines
Access to patients
Level of uncertainty
Shifting goalposts
Originator defence (e.g. subcutaneous formulations)
Changing standard of care
Next generation therapies
Payer clawbacks
Specialist markets
Unfamiliar propositions
Special biologics e.g. cell and gene therapies, immunoglobulins
Unusual forms of distribution e.g. ultra-cold chain
Platform technologies e.g. ADC, lipid nanoparticles
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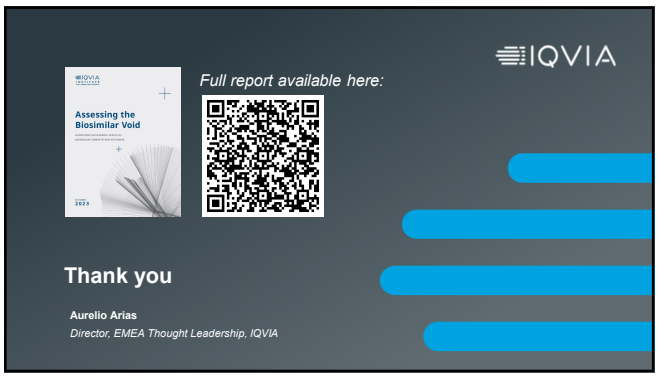
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Full report available here:
Thank you
Aurelio Arias
Director, EMEA Thought Leadership, IQVIA

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Vzdržnost zdravstvenega sistema in uspešna implementacija podobnih bioloških zdravil v Sloveniji: Kako doseči oboje?

How to make biosimilars a sustainable success in Slovenia

Jurij Fürst

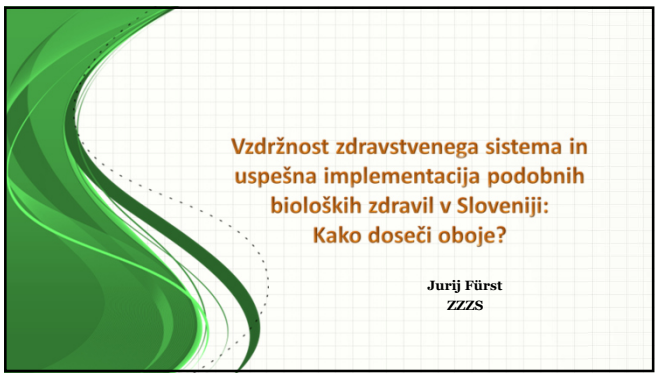
Zavod za zdravstveno zavarovanje Slovenije

Povzetek

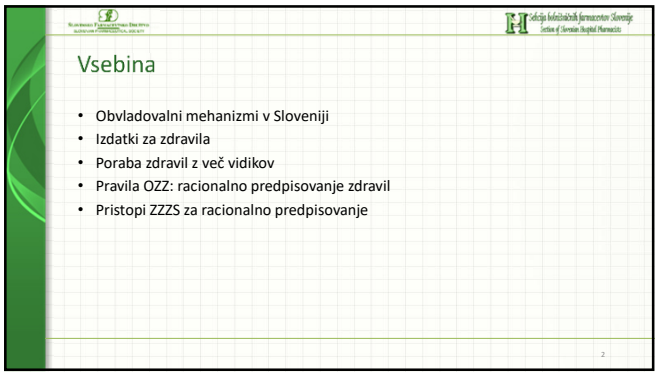
Pravila obveznega zdravstvenega zavarovanja (OZZ) določajo, da zdravnik izbere med zdravili v isti farmakološki skupini zdravilo z najboljšo stroškovno učinkovitostjo, med zdravili z enako učinkovino pa najcenejše na slovenskemu trgu dostopno zdravilo. Uporabo dražjih paralel je torej treba utemeljiti s kliničnim stanjem bolnika, pri katerem cenejša paralela iz kliničnih razlogov ne more biti uporabljena. S prihodom generikov in podobnih bioloških zdravil, za katera Zavod doseže ob razvrstitvi na seznama A in B bistveno nižje cene, imajo bolnišnice in drugi izvajalci na voljo paralele z različnimi cenami. Ustrezno izveden javni razpis zato omogoči velike prihranke Zavodu in s tem olajša razvrščanje novih zdravil. Žal se pogosto dogaja, da se nove, cenejše paralele ne uporabljajo v takšnem obsegu, kot bi se lahko. ZZZS skuša osveščati strokovna združenja za čim večjo uporabo cenejših paralel, bolnišnice pa za pripravo preglednih, dobro zastavljenih javnih razpisov za zdravila.

Abstract

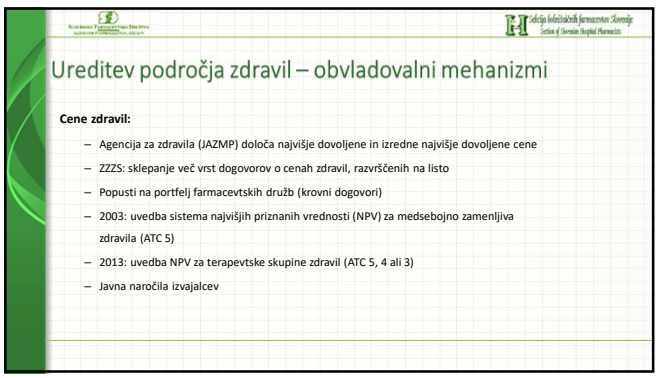
The rules of the Health Insurance Fund (ZZZS) stipulate that the doctor chooses the most cost-effective medicine among medicines in the same pharmacological group, and the cheapest medicine available on the Slovenian market among medicines with the same active ingredient. The use of more expensive parallels must therefore be justified by the clinical condition of the patient for whom the cheaper parallel cannot be used for clinical reasons. With new generics and biosimilars classified in Schedules A and B with significantly lower prices, hospitals and other providers have access to parallels with different prices. A properly executed tender therefore allows for significant savings for the ZZZS and thus facilitates the reimbursement of new medicines. Unfortunately, it is often the case that new, cheaper parallels are not used as much as they could be. The Health Insurance Fund is trying to raise awareness among professional associations to use cheaper parallels as much as possible and among hospitals to prepare transparent, well-designed tenders for medicines.


Vzdržnost zdravstvenega sistema in uspešna implementacija podobnih bioloških zdravil v Sloveniji: Kako doseči oboje?
Jurij Fürst
ZZZS

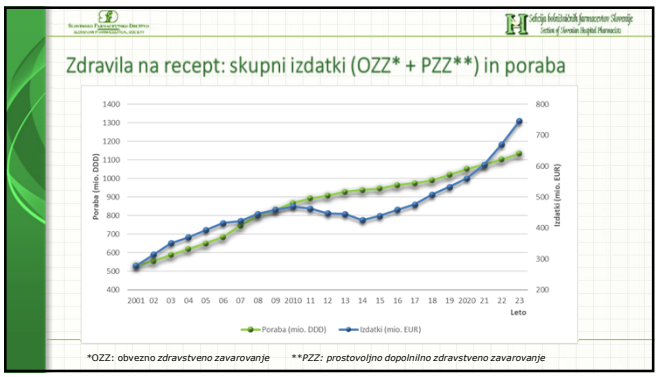
1


Vsebina
• Obvladovalni mehanizmi v Sloveniji
• Izdatki za zdravila
• Poraba zdravil z več vidikov
• Pravila OZZ: racionalno predpisovanje zdravil
• Pristopi ZZZS za racionalno predpisovanje

2


Ureditev področja zdravil – obvladovalni mehanizmi
Cene zdravil:
– Agencija za zdravila (JAZMP) določa najvišje dovoljene in izredne najvišje dovoljene cene
– ZZZS: sklepanje več vrst dogovorov o cenah zdravil, razvrščenih na listo
– Popusti na portfelj farmacevtskih družb (krovni dogovori)
– 2003: uvedba sistema najvišjih priznanih vrednosti (NPV) za medsebojno zamenljiva zdravila (ATC 5)
– 2013: uvedba NPV za terapevtske skupine zdravil (ATC 5, 4 ali 3)
– Javna naročila izvajalcev

3



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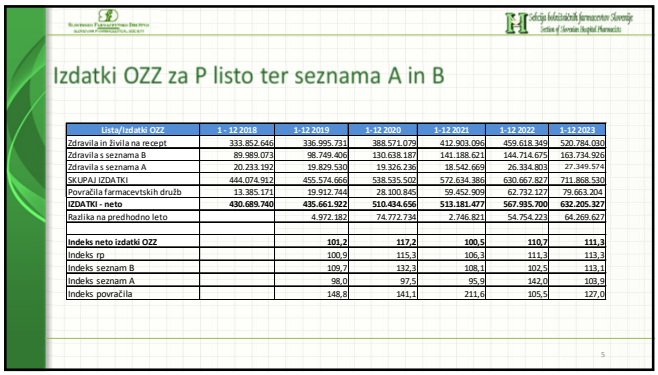

Lista/izdatki OZZ	1 - 12.2018	1-12.2019	1-12.2020	1-12.2021	1-12.2022	1-12.2023
Zdravila in živila na recept	333.852.646	336.995.731	388.571.079	412.903.096	459.618.349	520.784.030
Zdravila s seznama B	89.989.073	98.749.406	130.638.187	141.188.621	144.714.675	163.734.926
Zdravila s seznama A	20.233.192	19.829.530	19.326.236	18.542.669	26.334.803	27.349.574
SKUPAJ IZDATKI	444.074.912	455.574.666	538.535.502	572.634.386	630.667.827	711.868.530
Povračila farmacevtskih družb	13.385.171	19.912.744	28.100.845	59.452.909	62.732.127	79.663.204
IZDATKI - neto	**430.689.740**	**435.661.922**	**510.434.656**	**513.181.477**	**567.935.700**	**632.205.327**
Razlika na predhodno leto		4.972.182	74.772.734	2.746.821	54.754.223	64.269.627
Indeks neto izdatki OZZ		**101,2**	**117,2**	**100,5**	**110,7**	**111,3**
Indeks rp		100,9	115,3	106,3	111,3	113,3
Indeks seznam B		109,7	132,3	108,1	102,5	113,1
Indeks seznam A		98,0	97,5	95,9	142,0	103,9
Indeks povračila		148,8	141,1	211,6	105,5	127,0

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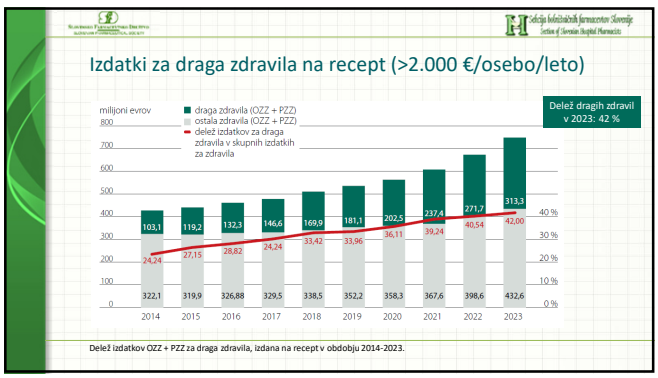

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Nekaj podatkov o zdravilih v OZZ v letu 2023

- Delež prebivalcev, ki so prejeli vsaj 1 Rp (2021): 74 %
- Porast v obdobju 2004 – 2023:
  - št. prejemnikov: + 8 %
  - porabe zdravil na prejemnika: 183 % (2x)

	2023	
Število zdravil na receptni listi (število učinkovin)	3.362	(906)
Število receptov na prebivalca	9,2	
Število pakiranj na prebivalca	19,2	
Izdatki OZZ za zdravila na Rp na prebivalca	238 €	
Izdatki OZZ* + PZZ** za zdravila na Rp na prebivalca	352 €	
Izdatki OZZ za zdravila s seznamov A + B na prebivalca	90 €	

*OZZ: obvezno zdravstveno zavarovanje
**PZZ: prostovoljno dopolnilno zdravstveno zavarovanje

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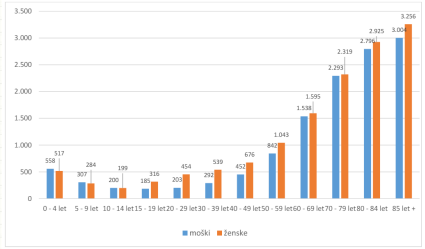
Predpisovanje zdravil po starostnih skupinah in po spolu v l. 2023*



Število izdanih receptov /100 prebivalcev po starostnih skupinah in spolu, Slovenija, 2023.

*http://www.nijz.si

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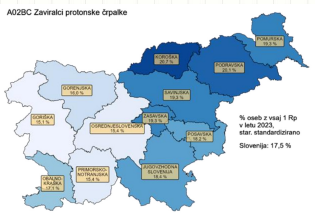
Velike razlike med regijami: Predpisovanje ZPČ v letu 2023*



Odstotek oseb, ki jim je bil predpisan zaviralec protonske črpalke (A02BC) v posamezni statistični regiji R Slovenije v letu 2023.

* http://www.nijz.si

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