ŠÚKL
ŠTÁTNY ÚSTAV PRE KONTROLU LIEČIV

LIEKOVÁ POLITIKA A REGISTRÁCIA LIEKOV – pohľad ŠÚKL a výstupy pre farmakoekonomiku

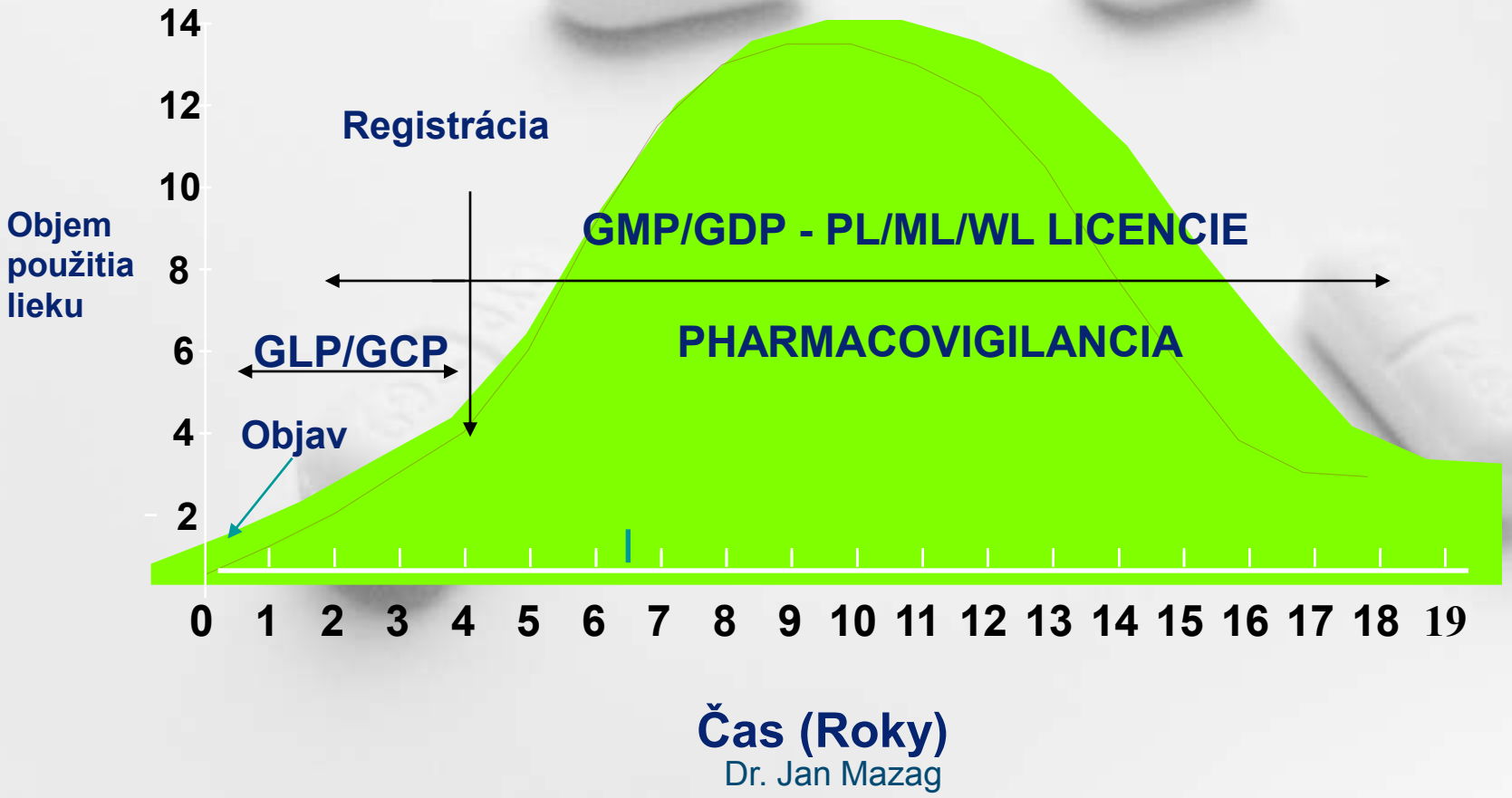
Jún, 2012

Market Access seminars, Pharmacoeconomics

PharmDr. Ján Mazag, vedúci služobného úradu a riaditeľ ŠÚKL

ŠÚKL činnosť - schéma

Životný cyklus lieku



Dr. Jan Mazag

Medicínske(farmaceutické) produkty sú regulované rôznymi postupmi podľa špecifickej jurisdikcie na navrátenie zdravia pacientov:

- LIEKY
- Zdravotnícke pomôcky
- Diagnostiká
- Inovatívne liečebné postupy

HTA znamená ďalšie intervencie pre účely kategorizácie:

- všetko pre určenie účinnosti, bezpečnosti a kvality + skríning, porovnanie oproti iným postupom, imunizačné programy, servis distribúcie, ekonomická nákladovosť a podobne. ...

Ciele regulácie/registrácie

Registrácia používa výskum a legislatívu na použitie k ochrane zdravia /liečbu chorôb na základe:

- Posúdenia kvalitatívnych parametrov
- Poznania nežiaducich účinkov a ich akceptácie
- Posúdenia účinnosti (v RCT, oproti placebu +/- aktívneho komparátora)

Z perspektívy pacienta a verejného zdravia:

- Vzťah účinku a bezpečnosti v definovanej cieľovej skupine pacientov, t.j. efektivita a ‘bezpečnosť ’ pri definovanom použití.
- Podpora inovácie

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Ciele HTA

- Účinnosť a nákladová efektivita pri definovanom použití (lieku)

Cieľ pre umožnenie dostupnosti pre pacientov (rozhodnutie o celkovom používaní)

- Maximalizácia získaného zdravia pri definovanej výške zdrojov, pri zohľadnení HTA ale tiež určených priorít, potrieb, znalostí a zdrojov v kontexte danej krajiny

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Interakcia medzi reguláciou(registráciou) a HTA

1. Požiadavka na účinnosť lieku a zdieľanie informácií o získaných dôkazoch o účinnosti lieku,

2. Spoločný záujem na minimalizácií nákladov na získanie informácií o dôkazoch,

3. Snaha o kompatibilitu odporúčaní pre zdravotníckych pracovníkov a pacientov pri správnom používaní lieku.

Efektivita (a ‘bezpečnosť”) pre účely HTA

- Vzťahuje sa na navrátenie zdravia dosiahnuté farmakoterapiou pri určenom spôsobe použitia

- V praxi sa môže zásadne líšiť od účinnosti (a bezpečnosti) oproti placebu a optimálnym podmienkam dokladovaným v RCT
  - » Správne dávkovanie, dlžka a frekvencia použitia
  - » Charakteristiky pacientov
  - » Co-prescripcia, co-morbidity

Príklad: COX-2 inhibitory, sibutramin, dronedaron, pio, rosi

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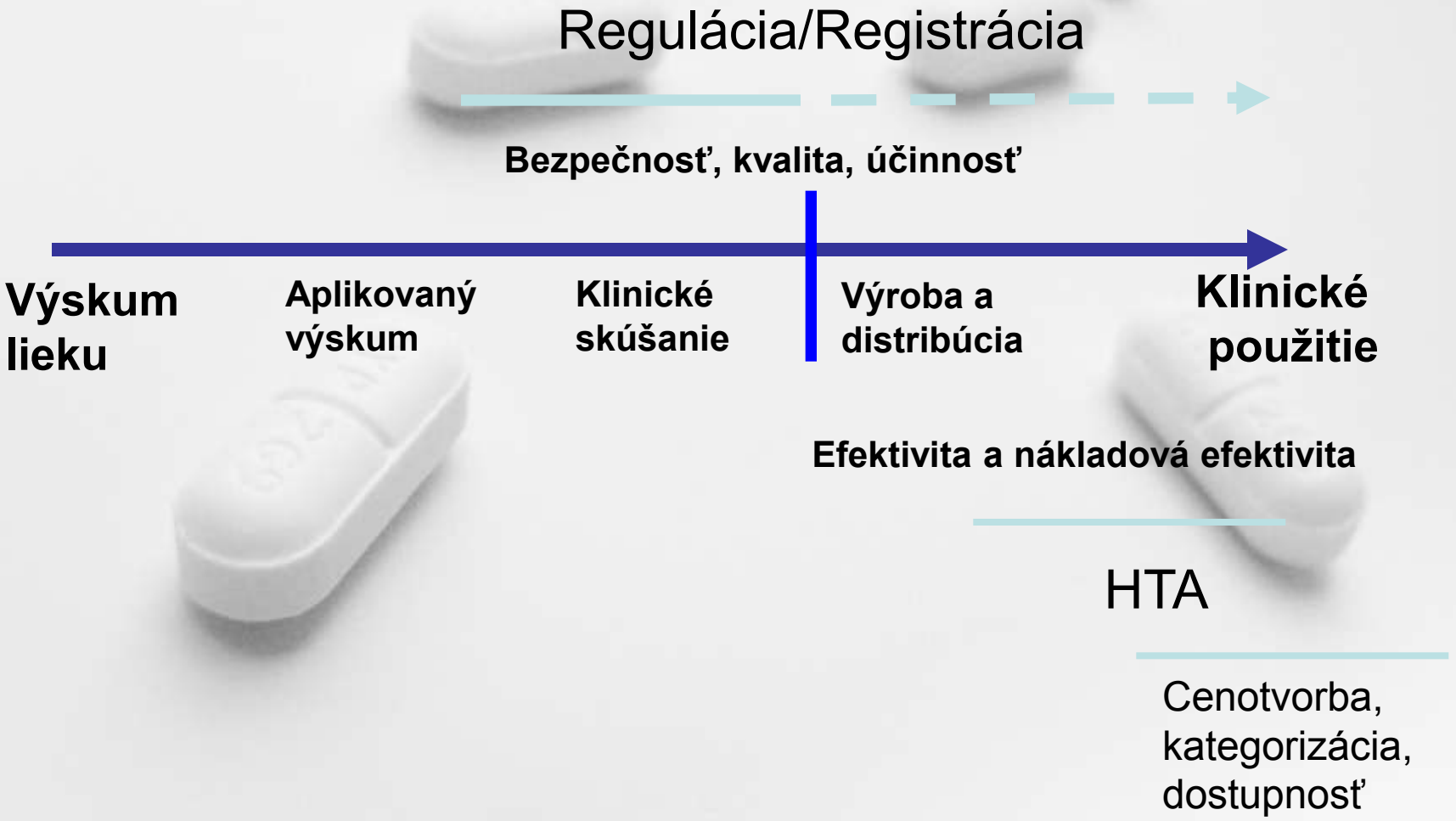
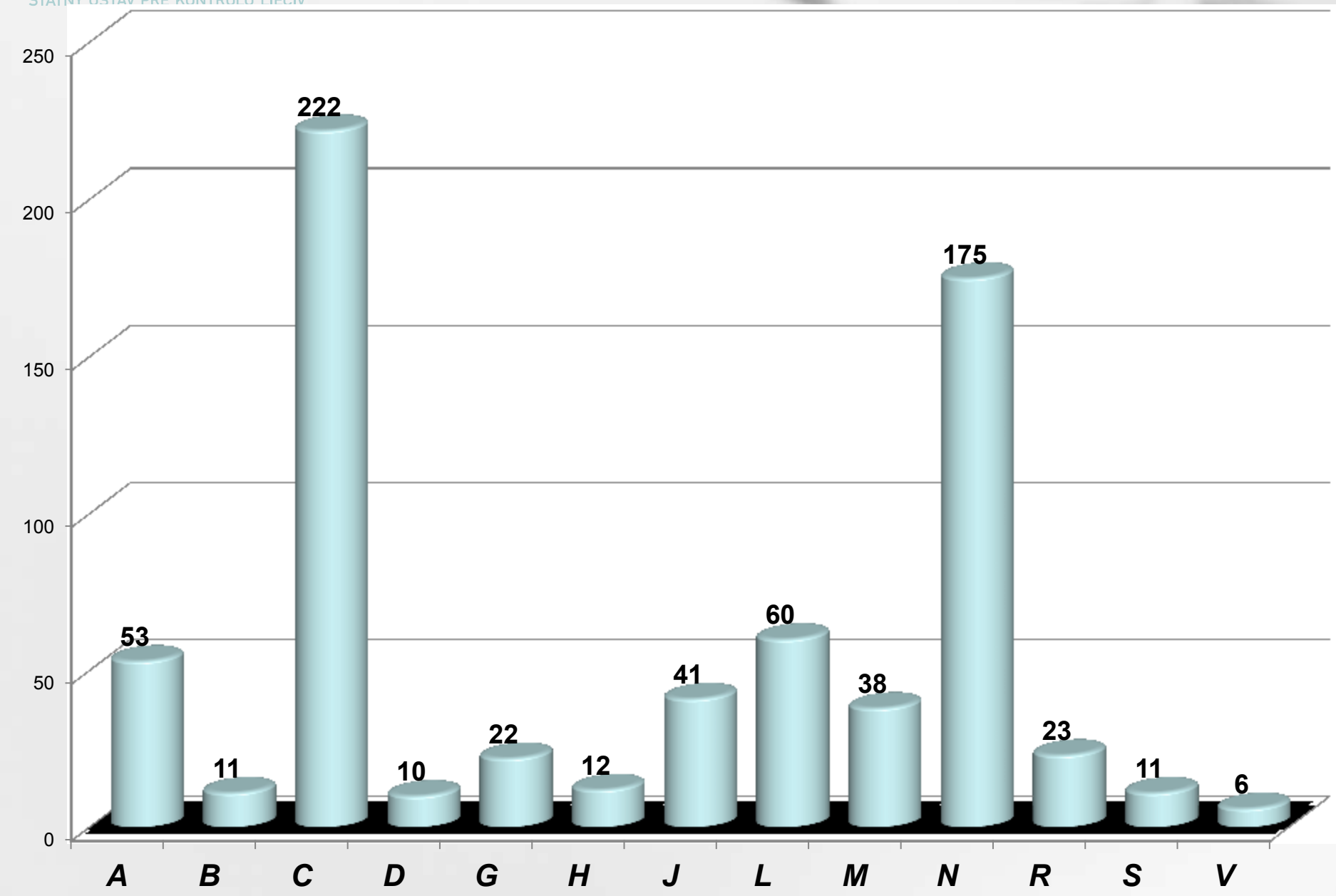
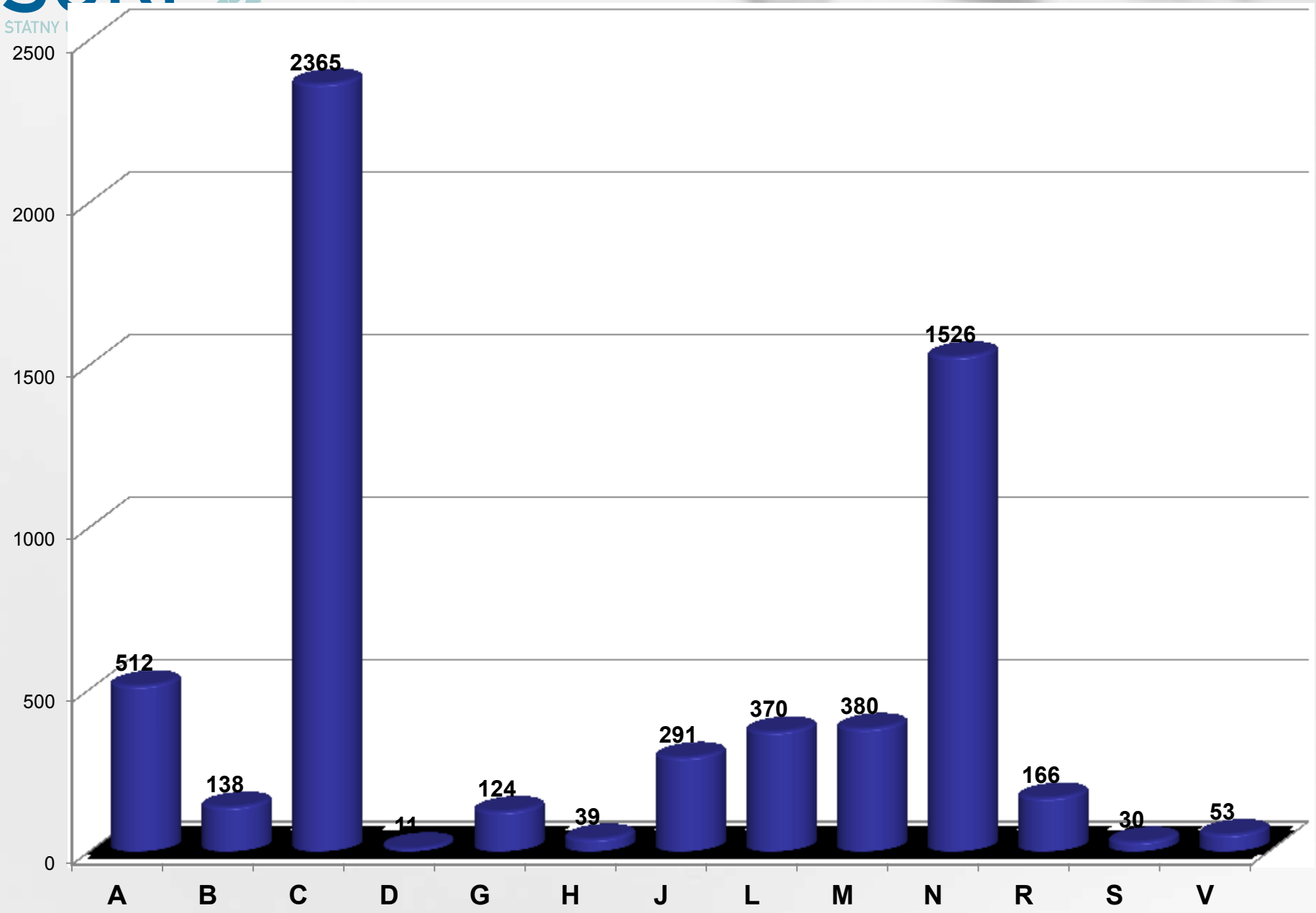
Životný cyklus lieku



Počet vydaných rozhodnutí o registrácií v roku 2011 podľa ATC prvej úrovne



Počet liekov registrovaných v roku 2011 podľa ATC prvej úrovne



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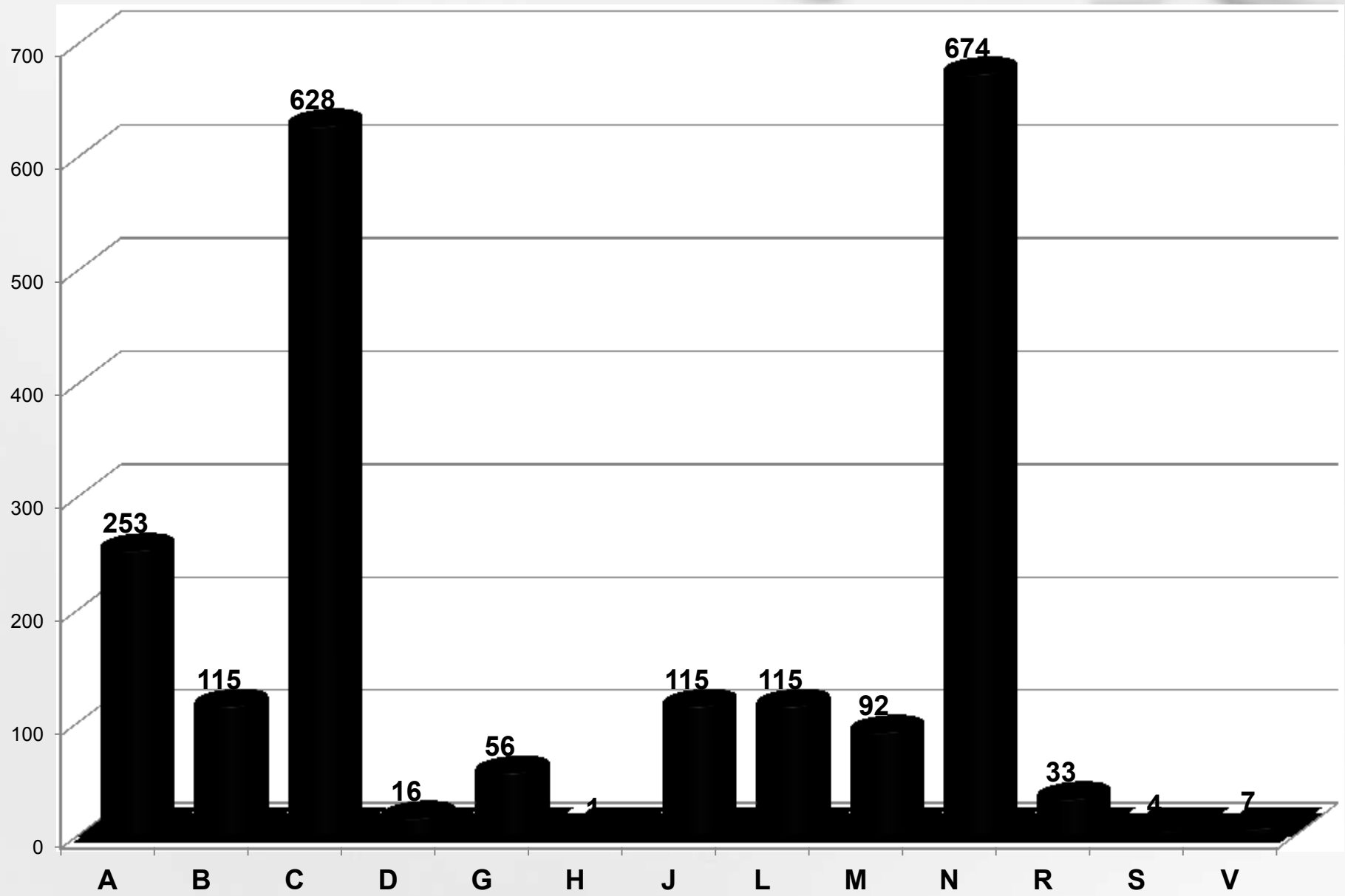
Počet deregistrovaných liekov v roku 2011 podľa ATC prvej úrovne



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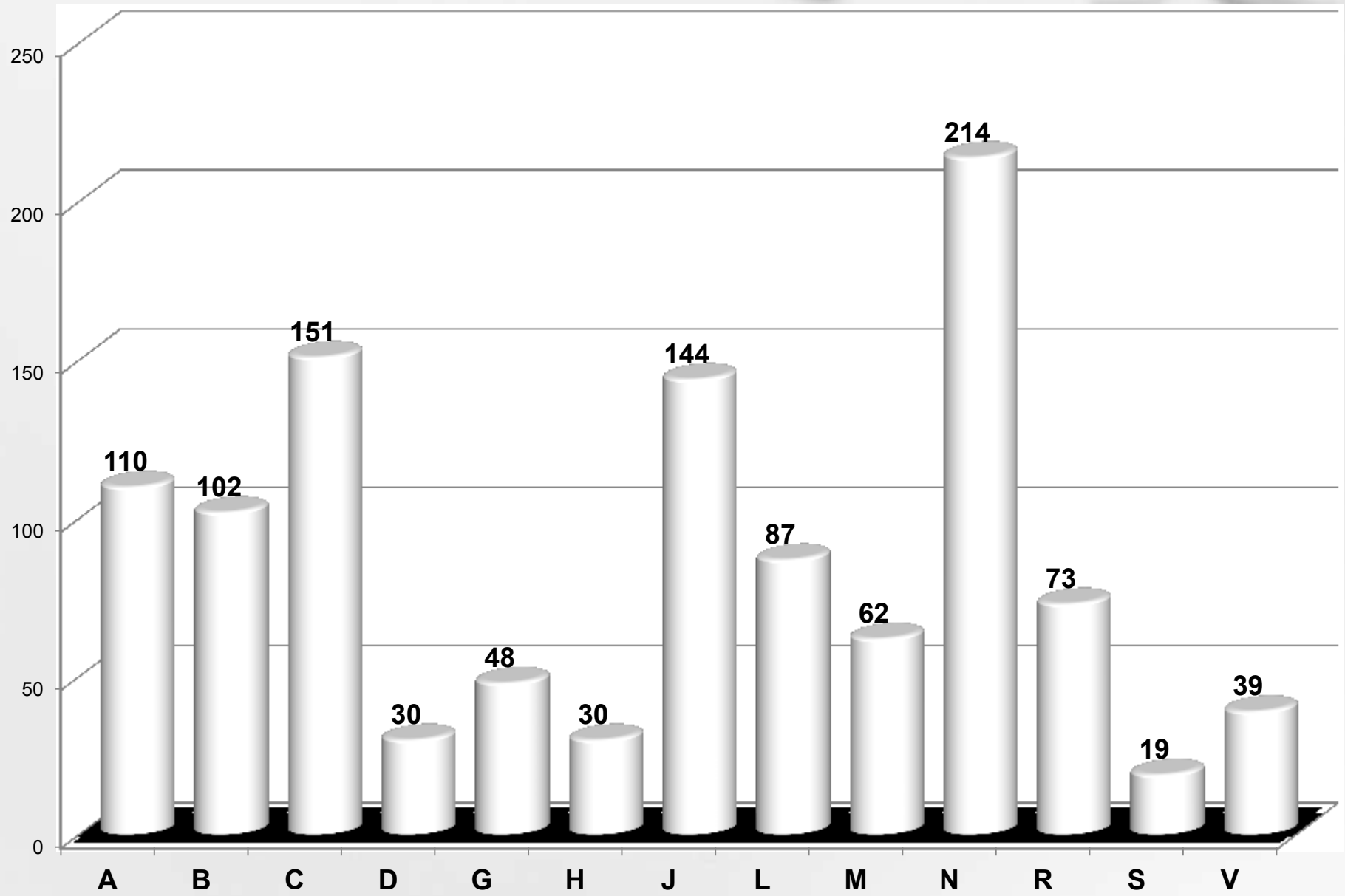
Počet vybavených žiadostí o zmenu typu II. v roku 2011 podľa ATC prvej úrovne



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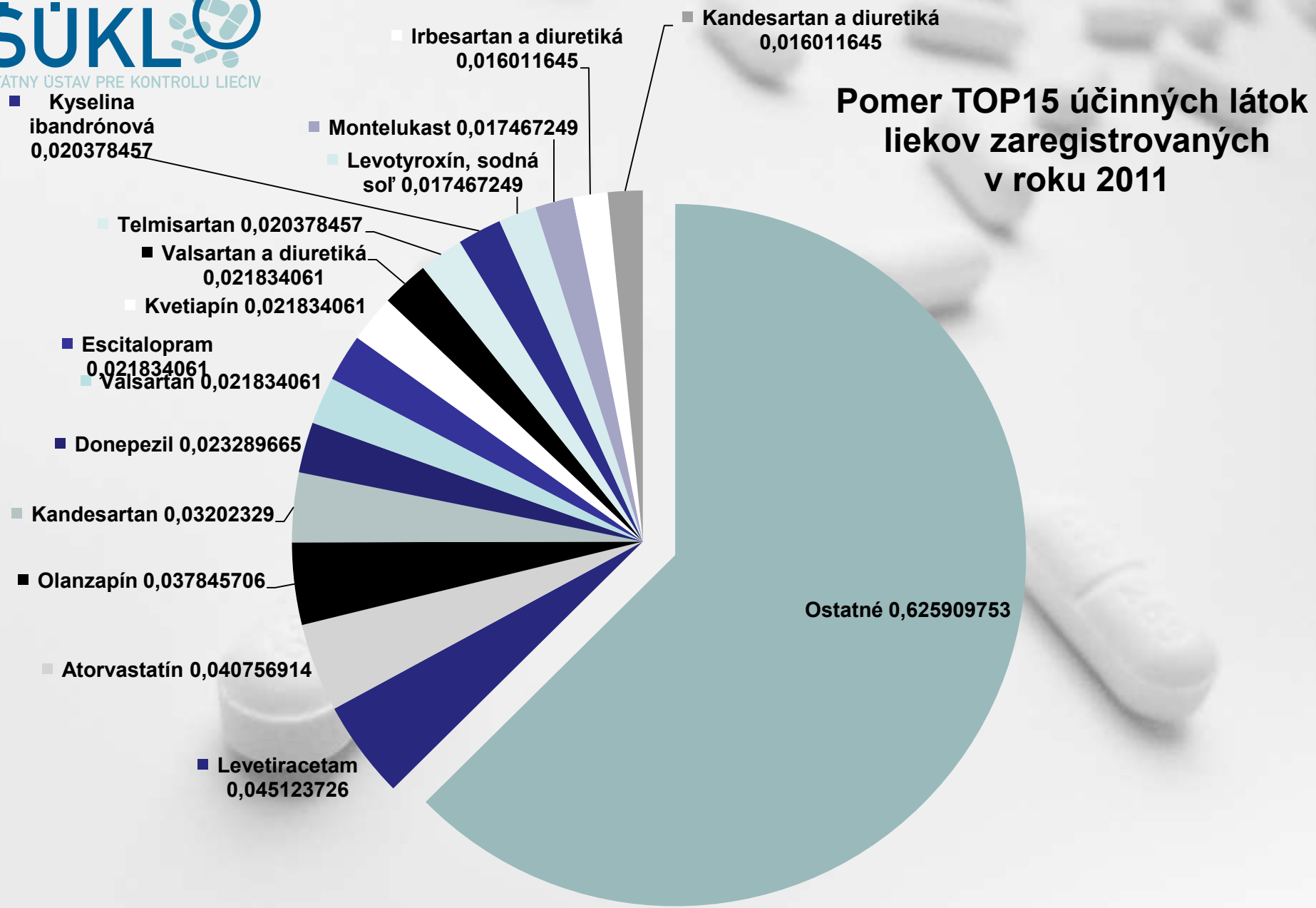
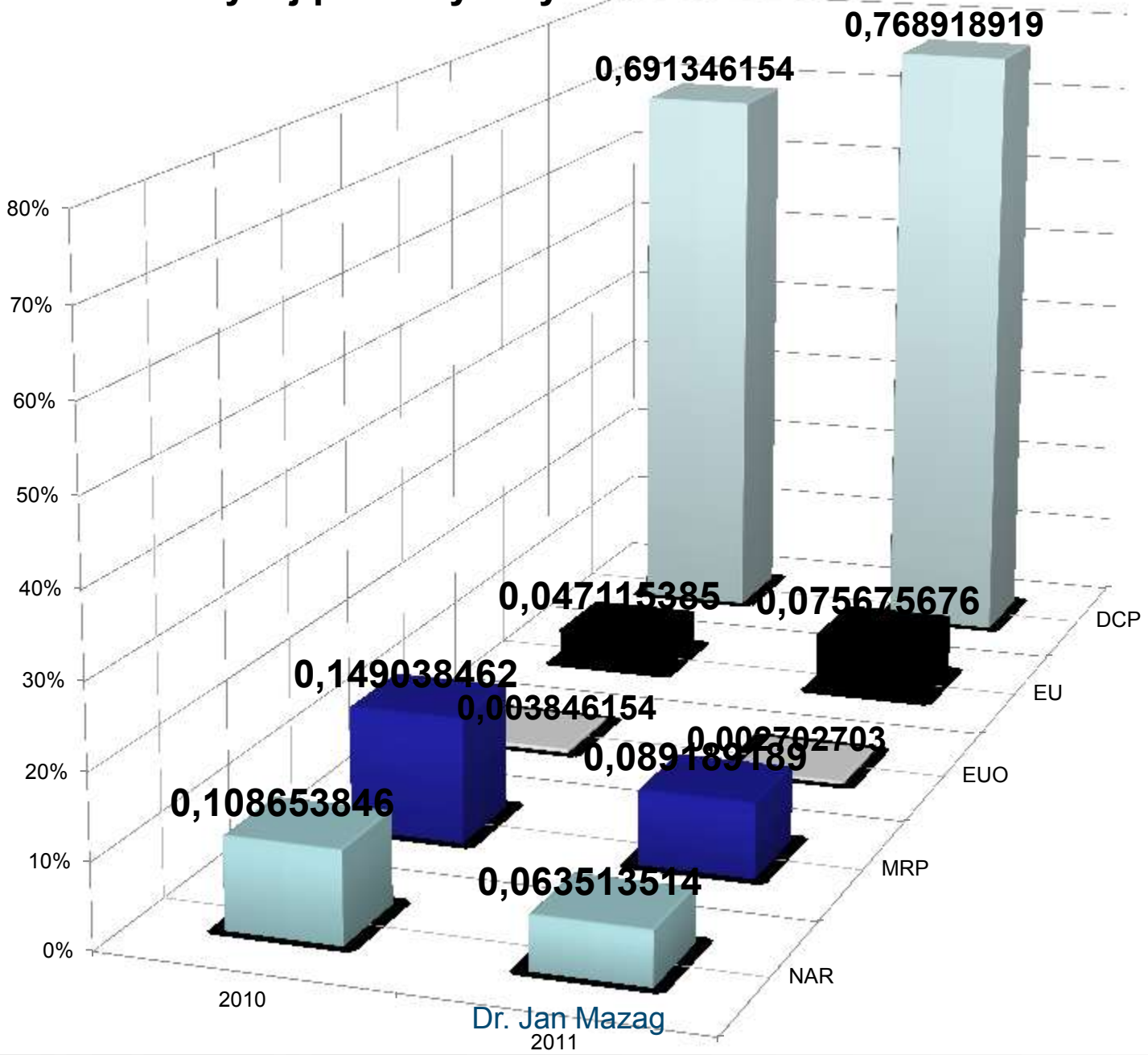
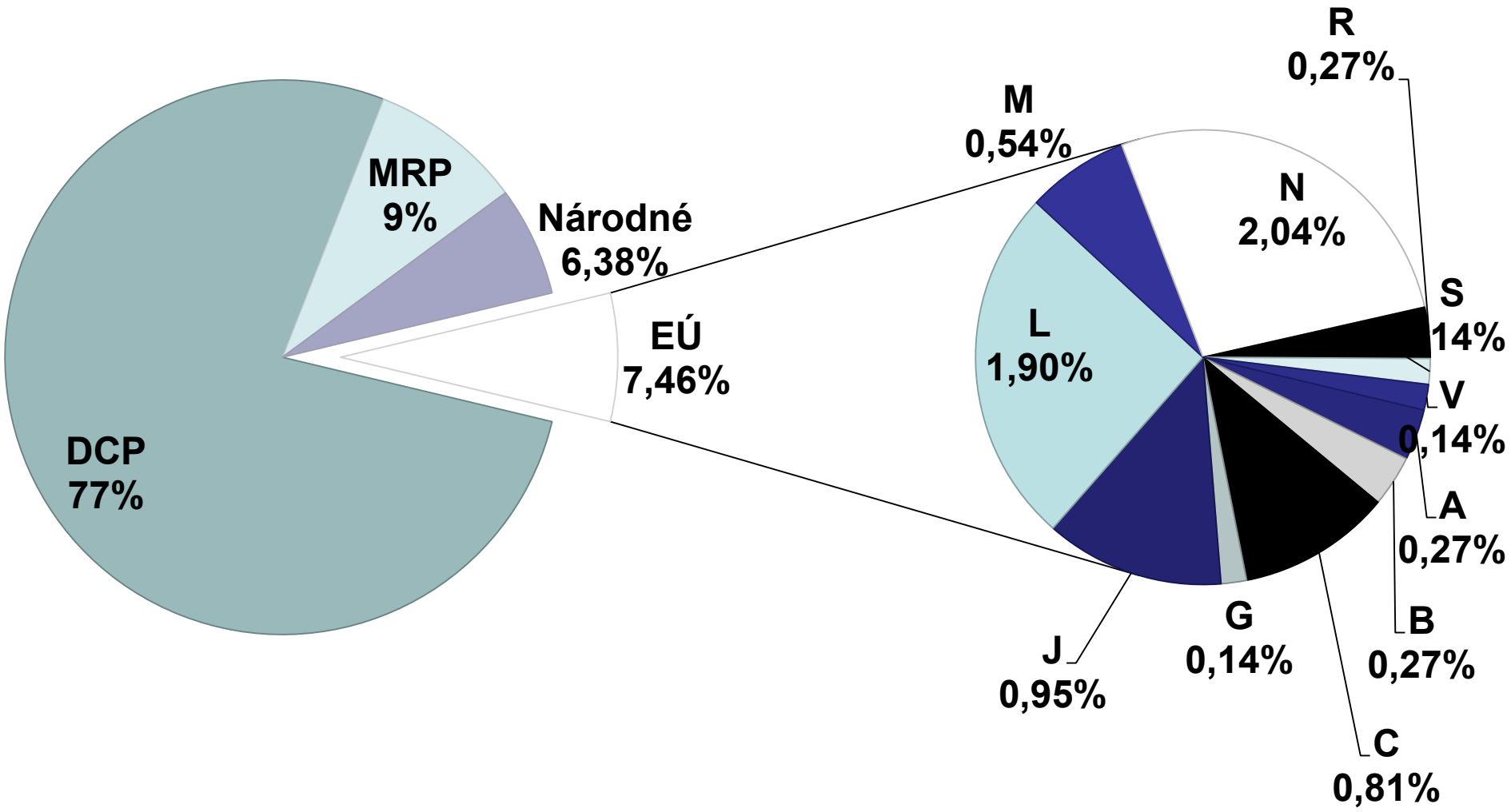
Pomer TOP15 účinných látok liekov zaregistrovaných v roku 2011



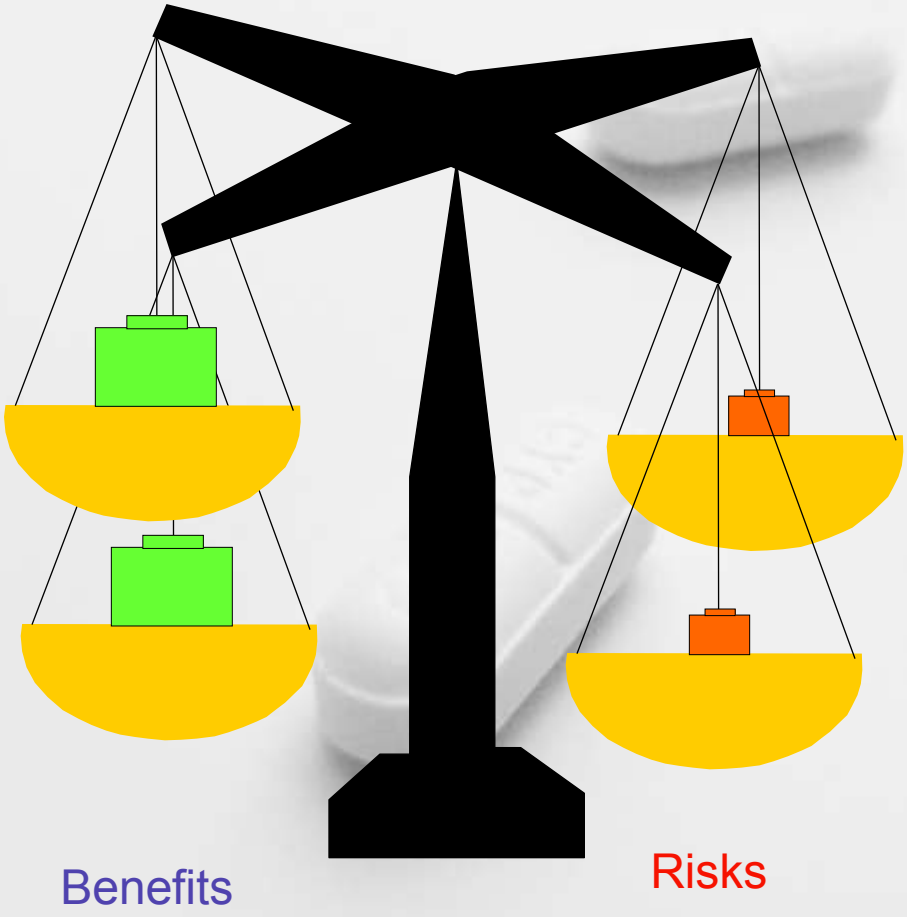
Vývoj počtu vydaných rozhodnutí medzi rokmi 2010 a 2011



Vydané rozhodnutia 2011 podľa typu registrácie, detailizácia EÚ registrácií podľa ATC

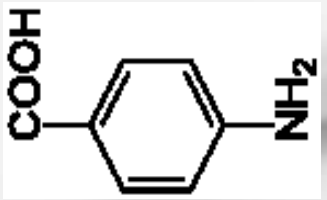
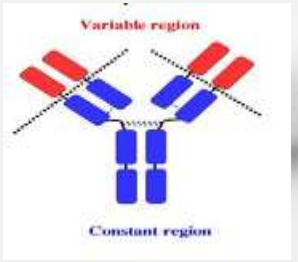
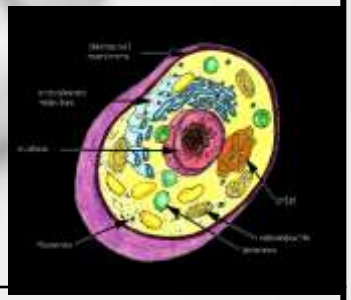


Mení sa prístup k hodnoteniu účinok / riziko v liekových agentúrach?



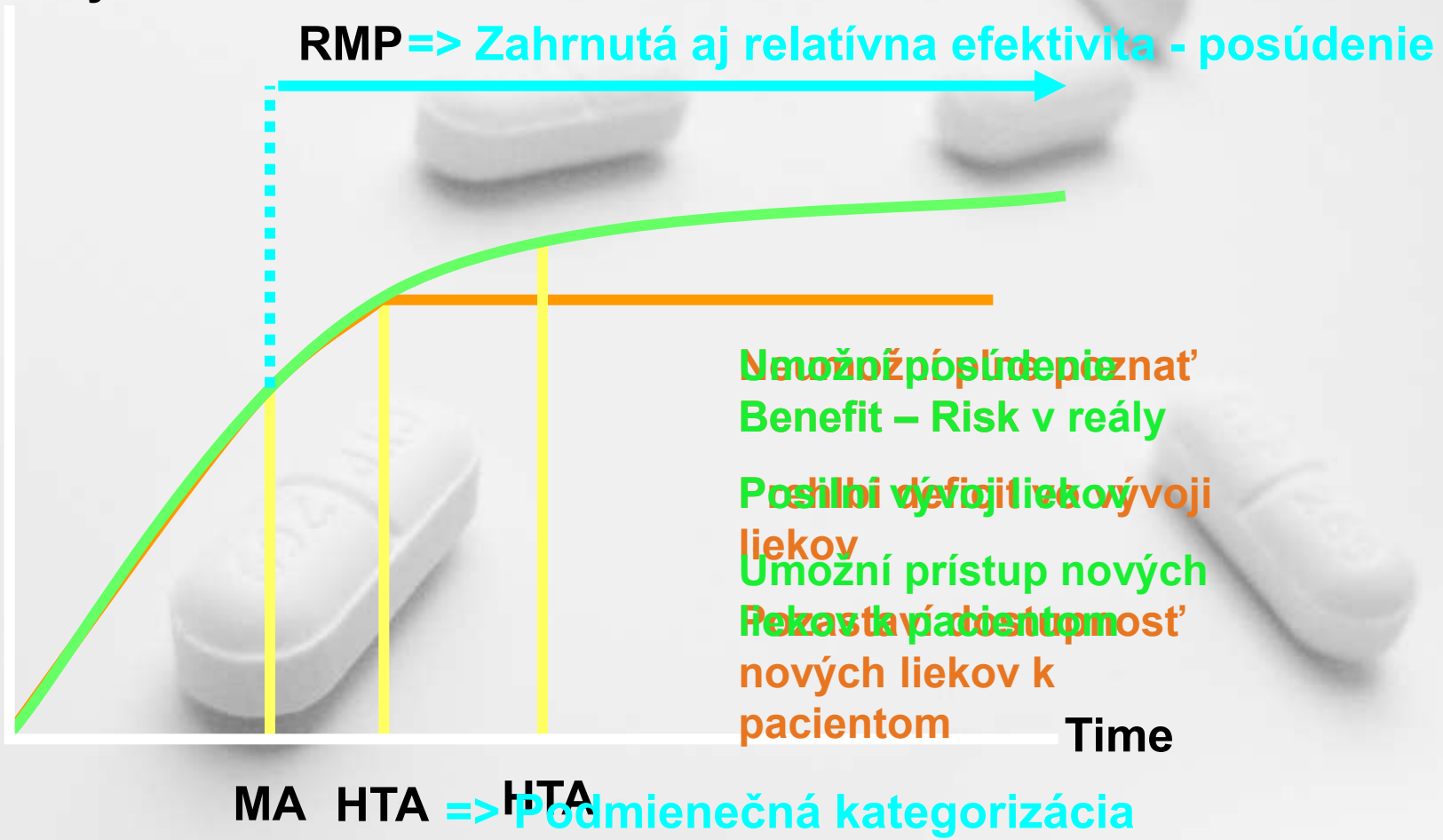
- Risk averzia: znamená nižšia akceptácia rizika pre daný účinok, t.j. znižuje sa "ochota obchodovať s pomerom"
- Komplikovaný rozhodovací proces
- Nie kvantitatívne data o B-R hodnote

Základné charakteristiky klinických štúdií Phase III (EBM)

			
Indication	hypertension	rheumatoid arthritis	autologous chondrocyte implantation
N Patients	Approx. 8.000	600	120
Control group	placebo, active control	placebo, active control	Microfracture
Primary endpoint	Median diastolic BP	Symptoms Structure (Xray)	Symptoms Structure/histology
Blinding	yes	yes	no

RMP – Relatívna efektivita

Poznatky



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COLORECTAL CARCINOM

Active substance	Indication and date of registration	Efficacy
capecitabin **L01XE01** **L01BC06** **Xeloda** Pro-drug 5-FU Orally admin. CVS preclinical better than 5-FU	-- first-line monotherapy of patients with metastatic colorectal cancer→registered from **02/2001** -- adjuvant treatment of patients following surgery of stage III colon cancer →type II var **03/2005** -- treatment of metastatic colorectal cancer → type II var. **01/2008** -- first-line treatment of advanced gastric cancer in combination with a platinumbased regimen → type II var. **03/2007** -- the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy (in combination with docetaxel). -- as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. → Type II var. **03/2002**	**Colorectal CA –** 376 000 new cases each year in Europe – 5% of EU population is affected during his life spam Previous therapy – 5-fluorouracil, alone or in comb. with leucovorin Capecitabine non-inferiority proven 1. (PFS 241 days, OS-577days) vs 5 FU/leucovorin PFS-259 days, OS-549days) 2. ORR 25% capecitabin vs 16% MAYO) 3. QoL some tendency, no impressive 4. No cross comparison mon and others **Breast CA –** 300 000 new cases each year 1st line therapy – anthracyclines, then taxanes, then trastuzumab 1. Med surv 442 vs 352 days docetaxel 2. ORR 41% vs 30% in docetaxel 3. PFS 186 vs 128 taxanes 4. Med surv 163 a PFS 384 vs 93 in mono, 23% ORR, QoL higher

Dr. Jan Mazag

COLORECTAL CARCINOM

Active substance	Indication and date of registration	Efficacy
cetuximab **L01XC06** **ma** **Erbitux**	→registered from **06/2004** -- treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS **wild-type metastatic colorectal cancer** (KRAS added **07/2008**) • in combination with chemotherapy, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan -- treatment of patients with **squamous cell cancer of the head and neck** • in combination with radiation therapy for locally advanced disease,→ type II var. **03/2006** • in combination with platinum-based chemotherapy for recurrent and/or metastatic disease → type II var. **11/2008**	**Metastatic colorectal CA –** 950 000 new cases per year Backbone therapy: 5-FU/leucovorin (LV) (including new variants), oxaliplatin and irinotecan OPUS study, other data coming in later, -- patients lived for longer without their disease getting worse when they received cetuximab in addition to chemotherapy 9.9 months vs. 8.7 months (irinotekan); 7.7 months vs. 7.2 months (oxaliplatin) **Sqamous cell CA** Mainstream therapy – radiotherapy, 5-FU, platinum analoques OS: 29.3 months (RT) vs. 49 months (RT+cetuximab) PFS: 12,4 months (RT) vs. 17,1 months (RT+cetuximab)

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ŠTÁTNY ÚSTAV PRE KONTROLU LIEČIV

COLORECTAL CARCINOM

Active substance	Indication and date of registration	Efficacy
Panitumumab L01XC08 ma **Vectibix**	monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens → **registered 12/2007** **Combination therapy in mCRC with FOLFIX and FOLFIRI 2011/03 as in cetuximab and bevacizumab**	**Colorectal CA –** 700 000 new cases each year in the world – 5% of EU population is affected during his life spam State of art therapies: irinotekan or oxaliplatin in comb. 5-FU/leucovorin (schema Mayo clinic) OS: 6,3 mo (best supportive care + panitumumab) vs. 6 mo (best supportive care) PFS: 8 weeks (best supportive care + panitumumab) vs. 7,3 weeks (best supportive care) Evaluated – in March 2011 negative, still process ongoing, inconsistency in data, size-specific, HR differences compared to cet,

COLORECTAL CARCINOM

bevacizumab **L01XC07 ma** **Avastin**	-- in combination with fluoropyrimidine-based chemotherapy -- for treatment of patients with **metastatic carcinoma of the colon or rectum** → **reg. 01/2005** -- in combination with paclitaxel or docetaxel -- for first-line treatment of patients with **metastatic breast cancer** → Type II var. **03/2007** -- in addition to platinum-based chemotherapy -- for first-line treatment of patients with unresectable advanced, metastatic or recurrent **non-small cell lung cancer** other than predominantly squamous cell histology → type II var **08/2007** -- in combination with interferon alfa-2a -- for first line treatment of patients with advanced and/or metastatic **renal cell cancer** → type II var **12/2007** -- indication „in combination with docetaxel for treatment of metastatic breast cancer“ deleted → 04/2011	**Colorectal CA –** 334 000 new cases each year in Europe – 5% of EU population is affected during his life spam PFS: 6,24 mo (placebo) vs. 10,55 mo (bev.) OS: 15,6 mo (placebo) vs. 20,3 mo (bev.) **Breast CA –** PFS: 8,2 mo (placebo) vs. 10,1 mo (bev.) OS: 89 mo (pl) vs. 92 mo (bev.) **Lung CA –** 1 mil. of new cases each year Standard therapy: platinum-based PFS: 5,4 mo (placebo) vs. 10,2 mo (bev.) OS: 10,3 (pl) vs. 12,3 mo (bev.) **Renal CA –** 2% from all solid tumors Incidence in EU – 11,04 (male) and 5,04 (female) per 100000 Standard treatment: IFN-alpha with vinblastine PFS: 5,4 mo (placebo) vs. 10,2 mo (bev.) OS: 19,8 (pl) vs. N/A mo (bev.) -- only a non-significant improvement of PFS -- potential detrimental effect on OS cannot be ruled out

SÚKL
STÁTNY ÚSTAV PRE KONTROLU LIEČIV

RENAL CELL CA

Active substance	Indication and date of registration	Efficacy
Sunitinib (Sutent)	→ registered from **07/2006** -- treatment of unresectable and/or metastatic **malignant gastrointestinal stromal tumour** (GIST) after failure of imatinib mesilate treatment due to resistance or intolerance. -- treatment of advanced/metastatic **renal cell carcinoma (MRCC)** → Conditional approval changed into normal in **01/2007** -- treatment of unresectable or metastatic, well-differentiated **pancreatic neuroendocrine tumours** with disease progression → **01/2011**	**GIST:** 1% of all GI tumors (incidence 7-15 cases per million) -- treatment: surgery, imatinib mesylate PFS: 24,6 weeks (sun) vs. 6,4 weeks (placebo) **Renal cell CA:** Incidence in EU – 11,04 (male) and 5,04 (female) per 100000 Therapy – IFN-alpha, IL-2 PFS: 47,3 weeks (sun) vs. 22 weeks (IFN-a) **Pancreatic NE tumors:** Incidence in USA – 0,38 (male) and 0,27 (female) per 100 000 Therapy – streptozocin, F-uracil, doxorubicin PFS: 11,4 mo (sun) vs. 5,5 mo (placebo)
Sorafenib (Nexavar) ORPHAN	→registered from **07/2006** for following indication: -- treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy -- treatment of hepatocellular carcinoma → type II var. **10/2007**	**Renal cell CA:** 2% of all adult malignant tumors Therapy – IFN-alpha, IL-2 PFS: 84 days (pl) vs. 167 days (sor.) OS: 15,9 months (pl) vs. 19,3 months (sor.) **Hepatocellucar CA:** 560 000 new cases/year Therapy: surgery, doxorubicine (not licensed, but used) OS: 34,4 weeks (pl) vs. 46,3 weeks (sor.) TTP: 12,3 weeks (pl) vs. 24,0 weeks (sor.)

RENAL CELL CA

Active substance	Indication and date of registration	Efficacy
Temsirolimus (Torisel) ORPHAN	-- first-line treatment of patients with advanced **renal cell carcinoma** who have at least three of six prognostic risk factors → registered from **11/2007** -- treatment of adult patients with relapsed and/or refractory **mantle cell lymphoma (MCL)** → type II var. **10/2009**	**Renal cell CA:** 2% of all adult malignant tumors Therapy – IFN-alpha, IL-2 PFS: 5,6 months (torisel) vs. 3,2 months (IFN-a) OS: 10,9 months (torisel) vs. 7,3 months (IFN-a) **MCL:** 8% of all lymphoma diagnosis Therapy – alkylating agent, anthracycline, vinca alkaloids, antimetabolites-no single-agent treatment available PFS: 4,8 months (torisel) vs. 1,9 months (other ther.) OS: 12,8 months (torisel) vs. 10,3 months (other ther.)
Everolimus (Afinitor) ORPHAN	-- treatment of patients with advanced **renal cell carcinoma**, whose disease has progressed on or after treatment with VEGF-targeted therapy → registered **08/2009**	**Renal cell CA:** more than 208 000 cases/ year worldwide Therapy – IFN-alpha, IL-2 PFS: 4,90 months (everolimus) vs. 1,87 months (placebo)

Authorised products in Renal cell carcinoma : overview of licensed products and outcomes from clinical trials

	Indication	Basis_efficacy	Efficacy_long
Afinitor (everolimus L01XE10) PKi	RCC 2nd line after TKI (from August, 3, 2009)	Ph3, RCT placebo-controlled (n=416) all risks Cross-over 80%	**PFS** 4.9 vs 1.9 months HR 0.33 (0.25-0.43) P>0.001 **OS** 14.8 vs 14.4 m
Torisel (temsirolimus L01XE09) PKi	RCC 1st line (from November, 19, 2007)	Ph3, RCT, 3arm vs IFN (and IFN/ Torisel) (n=626) Poor risk NO cross-over	**OS** 10.9 vs 7.3 m HR 0.66 (0.53-0.81) p= 0.008 **PFS** 5.5 vs. 3.1 m HR 0.63 (0.53 – 0.81) p<0.001
Nexavar (sorafenib L01XE05) PKi	RCC 2nd line (from July, 19, 2006)	Ph3, RCT placebo-contr. (n=903) cross-over 48%	**PFS** 5.5 vs 2.8 m HR 0.44 (0.35-0.55) p<0.01 **OS** (prior to cross-over) P=0.02 **OS (final)** 17.8 vs 15.2 m HR 0,88 (0.74-1.04) p= 0.146
Sutent (sunitib L01XE04) PKi	RCC 2nd line (conditional approval) (from July 19, 2006)	2 Ph2 single arm uncontrolled	**ORR** 25 % per independent review
Sutent (sunitinib L01XE04) PKi	RCC 1st line (from January, 10, 2007)	Ph3 RCT vs IFN (n= 750) Cross-over 33%	**PFS** 11 vs 5 m HR 0.42 (0.32-0.54) p<0.001 **OS** 26.4 vs 21.8 m HR 0.82 (0.67-1.00) P= 0.051
Avastin (bevacizumab L01XC07) Monoclonal antibody	RCC 1st line (from December 2007)	Ph3, RCT Avastin/ IFN vs IFN (n=649) Cross-over: yes	**PFS** 10.2 vs 5.4 m HR 0.63 (0.52-0.75) p<0.001 **OS** NR vs 19.8 m HR 0.79 (0.62-1.02) P= 0.067

Active substance	Indication and date of registration	Efficacy
Trastuzumab L01XC03 ma Herceptin	-- HER2 positive Metastatic Breast Cancer (MBC) a) as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease→ registered **05/2000** b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable → registered **05/2000** c) in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease → type II var. **06/2004** d) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab → type II var. **4/2007** -- treatment of HER 2 positive early breast cancer (EBC) following surgery, chemotherapy and radiotherapy → type II var. **5/2006** -- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel or as part of a treatment regimen in combination with docetaxel and carboplatin → type II var. **4/2011** -- in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients	**Breast CA:** Monotherapy herceptin -- TTP: 3,2 mo; OS: 16,4 mo In comb. with paclitaxel: TTP: 3 mo (pac) vs. 7,1 mo (pac+herc) OS: 17,9 mo (pac) vs. 24,8 mo (pac+herc) In comb. with docetaxel: TTP: 6,1 mo (doc) vs. 11,7 mo (doc+herc) OS: 22,74 mo (doc) vs. 31,2 mo (doc+herc) In comb. with anastrozole: PFS: 2,4 mo (ana) vs. 4,8 mo (ana+herc) OS: + 4,6 mo in ana+herc. group **Gastric CA:** PFS: 5,5 mo (stand. treatm.) vs. 6,7 mo (st. tr.+herc) OS: 11,1 mo (stand. treatm) vs. 13,8 mo (st. tr.+herc)

Active substance	Indication and date of registration	Efficacy
lapatinib L01XE07 Tyverb	Treatment of patients with breast cancer whose tumours overexpress ErbB2 (HER2). -- in combination with capecitabine for the patients with advanced or metastatic disease Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting → registered **06/2008** -- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy → type II var. **05/2010**	**Breast CA:** incidence – 350 000 new cases/year in EU Standard therapy: taxanes, anthracyclines, antimetabolites, aromatase inhibitors, antibodies Comb. with capecitabine TTP: 18,3 weeks (capecitabine) vs. 23,9 w (cap.+lapat.) OS: 65,9 weeks (capecitabine) vs. 74,0 w (cap.+lapat.) Comb. with letrozol: PFS: 35,4 weeks (lap. + letrozol) vs. 13,0 weeks (letrozol)
toremifen L02BA02 antiestrogén Fareston	First line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients. Fareston is not recommended for patients with estrogen receptor negative tumours → registere **02/1996**	
fulvestrant L02BA03 Faslodex	Faslodex is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant	**Breast CA:** incidence – 350 000 new cases/year in EU Standard therapy: taxanes, anthracyclines, antimetabolites,

Imatinib
L01XX28

(Glivec)

1) treatment of

a)adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy → registered **07/2001**

b)adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment → type II var. **12/2002**

c)adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.→ type II var. **12/2002**

d)adult patients with relapsed or refractory Ph+ ALL as monotherapy. → type II var. **09/2006**

e)adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. → type II var. **11/2006**

f)adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. → type II var. **11/2006**

2) is indicated for

a)the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) → type II var. **05/2002**

b)the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery → type II var. **09/2006**

c)the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment. → type II var. **04/2009**

CML: incidence – 1case/100 000 people per year

Standard therapy: bone marrow transplantation, IFN-alpha, cytosine-arabinose

Efficacy:

Indication 1a: -- 65% of pts. achieved major cytogenetic response

Indication 1c: Median survival 8 months with imatinib

Indication 1d: Major cytogenetic response rate 90%

Indication 1e: Overal survival 65 moths since diagnosis

Indication 1f: 21 from 65 pts achieved complete molecular remission with a median follow-up of 28 months

GIST: Incidence: 0,06 in 10 000 persons in the EU

Standard treatment: surgical, no approved specific drug therapy

Efficacy

Indication 2a:

TTF: 1,2 months (placebo) vs. 6 motnhs (imatinib)

Indication 2b: data on OS not sufficient, PFS more than 18 moths after imatinib

Indication 2c: Risk of recurrence reduced by 89% as compared to pl.

Dr. Jan Mazag

Active substance	Indication and date of registration	Efficacy
dasatinib L01XE06 Sprycel ORPHAN	→ registered **11/2006** for following indications: -- for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate. -- for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy. -- for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase → type II var. **12/2010**	**CML:** Incidence – 1case/100 000 people per year Standard therapy: bone marrow transplantation, IFN-alpha, cytosine-arabinose, imatinib **Efficacy:** CML: 2 year survival – 91% of pts treated with 100 mg dasatinib PFS: 4 months; OS: 8 months ALL: 2year survival – 95% of pst treated with 100 mg dasatinib Ph+ CML: Complete cytogenetic response rate within 12 months -- 77% dasatinib vs. 66% imatinib
nilotinib L01XE08 Tasigna ORPHAN	Tasigna is indicated for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. → registered **11/2007** In **12/2010** indication changed into: Tasigna is	**CML: i**ncidence – 1case/100 000 people per year Standard therapy: imatinib 49% of patients had a major cytogenetic response -- major molecular response rate in 12 mo was 44,3% (nilotinim)

Dr. Jan Mazag

Sibutramín – inhibítor spätného vychytávania serotonínu a noradrenalínu

-- indikovaný na podpornú liečbu v programe znižovania nadváhy:

-u obéznych pacientov s indexom telesnej hmotnosti (BMI) 30 kg/m^2 alebo vyšším;

-u obéznych pacientov s BMI 27 kg/m^2 alebo vyšším, ak sú prítomné s obezitou spojené rizikové faktory, ako diabetes typu 2 alebo dyslipidémia.

-- registrovaný a prehodnocovaný CHMP v r. 1999 a 2002 – pochybnosti ohľadom bezpečnosti (kardiovaskulárne NÚ) – výsledok prehodnocovania pozitívny, výrobca ale dostal post-registračnú podmienku

Postregistračná podmienka – vykonať klinickú štúdiu -- Sibutramine Cardiovascular OUTcomes – zameraná na bezpečnosť lieku u pacientov s kardiovaskulárnymi rizikovými faktormi:

-- dvojito zaslepená, randomizovaná, placebom kontrolovaná štúdia -- sibutramín 10mg/deň porovnávaný s placebom u pacientov nad 55 rokov, s KVS rizikom – 9805 randomizovaných pacientov

-- trvanie štúdie – 6 rokov

-- hodnotenie bezpečnosti a dlhodobého benefitu

-- u 11.4% (561/4906) pacientov liečených sibutramínom a 10.0% (490/4898) pacientov dostávajúcich placebo sa vyskytla KVS príhoda

-- SCOUT ukázala zvýšené KVS riziko pri sibutramíne (paradoxne, pri poklese hmotnosti by sa očakávalo znížené KVS riziko)

↓

-- 03/2010 -- CHMP – pozastavená registrácia sibutramínu

Dronedarón – multikanálový blokátor inhibujúci káliové kanály (vrátane IK(Ach), IKur, IKr, IKs) a teda predlžujúci akčný potenciál srdca a refraktérne periódy (trieda III), tiež inhibuje nátriové kanály (trieda Ib) a kalciové kanály (trieda IV), nekompetitívne antagonizuje adrenergné účinky (trieda II)

-- pred rokom 2011indikovaný u dospelých, klinicky stabilných pacientov s aktuálnou atriálnou fibriláciou (AF) s výnimkou permanentnej AF alebo s AF v anamnéze na prevenciu opätovného výskytu AF alebo na zníženie ventrikulárnej frekvencie

Registrácia (09/2009):

-- 5 štúdii s placebom a 1 s aktívnym komparátorom (amiodarón, štúdia ukázala, že DRO je menej účinný ako AMIO ako anti-arytmikum)

-- dronedarón znižoval výskyt kardiovaskulárnej hospitalizácie alebo smrti z akejkoľvek príčiny o 24,2 % v porovnaní s placebom

-- konzistentne oddialil čas do prvého opätovného výskytu AF/AFL (flutter)

-- bezpečnosť – lepší bezpečnostný profil ako amiodarón (s výnimkou NÚ KVS)

-- prijatý RMP – nutné extra PhV aktivity v porovnaní so štandardnými, nutné aktivity na minimalizáciu rizika

01/2011 – prehodnotenie bezpečnosti:

-- 2 hlásenia ťažkého poškodenia pečene u pacientov užívajúcich dronedarón

-- upozornenie do SPC, lekárom a pacientom, potreba prísnej kontroly funkcie pečene

-- 07/2011 – predčasné ukončenie PALLAS štúdie (hodnotenie benefitu 400mg dronedaronu BID pridaného k štandardnej liečbe u pacientov s permanentnou atriálnou fibriláciou a ďalšími rizikovými faktormi) – pacienti s dronedarónom viac príhod, hospitalizácii a srdcového zlyhania – rozšírenie prehodnotenia vzhľadom na nové dáta

-- 12/2011 – výledok: obmedzenie indikácie: udržanie sínusového rytmu po úspešnej kardioverzii u dospelých, klinicky stabilných pacientov s paroxyzmálnou alebo perzistujúcou atriálnou fibriláciou . Pre svoj bezpečnostný profil sa má predpisovať len po zvážení altenatívnych možností liečby. Multaq sa nesmie dávať pacientom, ktorí majú prekonané alebo aktuálne prítomné epizódy srdcového zlyhania alebo systolickú dysfunkciu ľavej komory

-- ďalšie zmeny v SPC (upozornenie o hepatotoxicite, toxicite pľúc), DHPC list, zmeny v edukačných materiáloch pre lekárov, program monitorujúci používanie lieku, použitie lieku iba špecializ. odborníkmi

Počas prehodnotenia ešte urobené nasledujúce zmeny:

-- 04/2011 – pridanie upozornenia do SPC, týkajúceho sa potreby monitorovania funkcie pečene pred a počas liečby

-- 05/2011 – pridanie interakcie dabigatran + dronedaron

-- 06/2011 – pridanie interakcie dronedaron + antagonisty vitamínu K

ĎAKUJEME ZA POZORNOSŤ

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