FARMAKOVIGILANČNÍ SIGNÁLY - NOVÉ MOŽNOSTI A POVINNOSTI DRŽITELŮ

Jana Koprušáková

Obsah prezentace

- Signal management obecně
- Novinky v managementu FV signálů
- Možnosti využití EVDAS pro detekci FV signálů, eRMR

Signal management

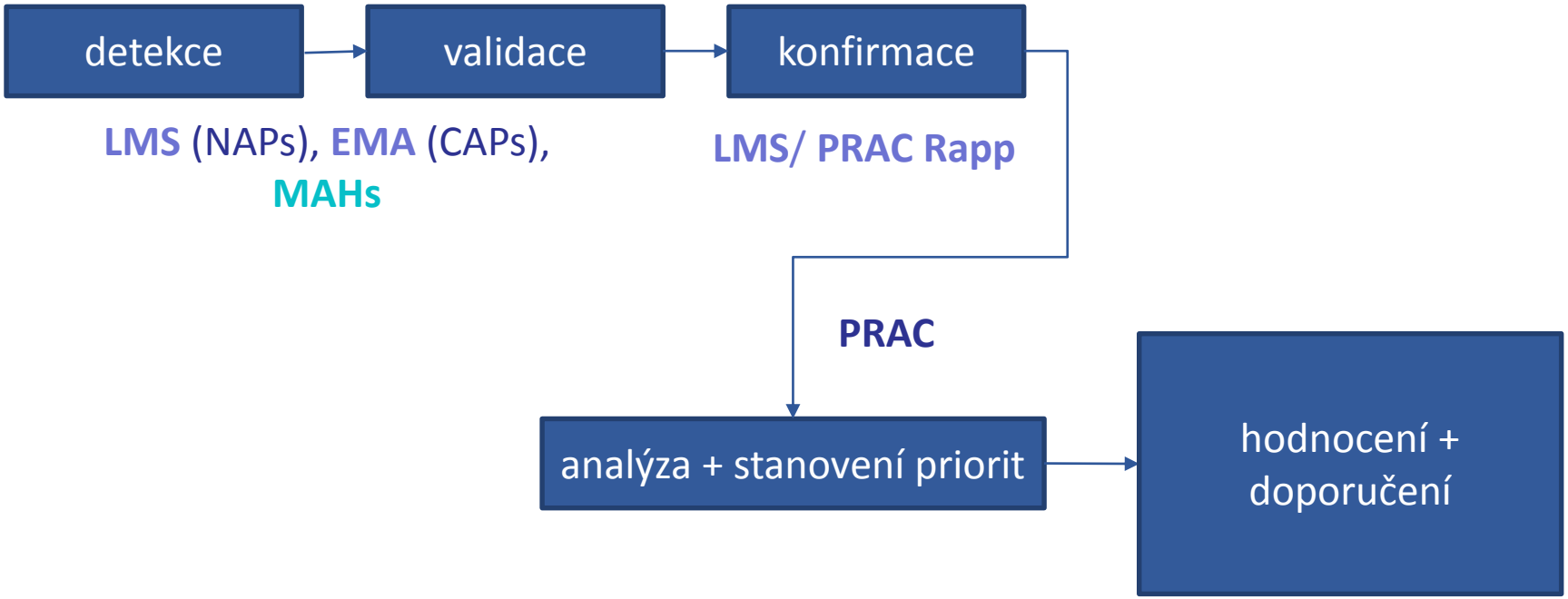
GVP Module IX
platí verze z r. 2012
Rev. 1 (draft) – vstoupí do platnosti s novou EudraVigilance

Addendum 1 to GVP Module IX (draft)

Questions & answers on signal management
srpen 2016

Signal management na stránkách EMA
www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

Signal management process - NCAs



Závěry jednání PRAC

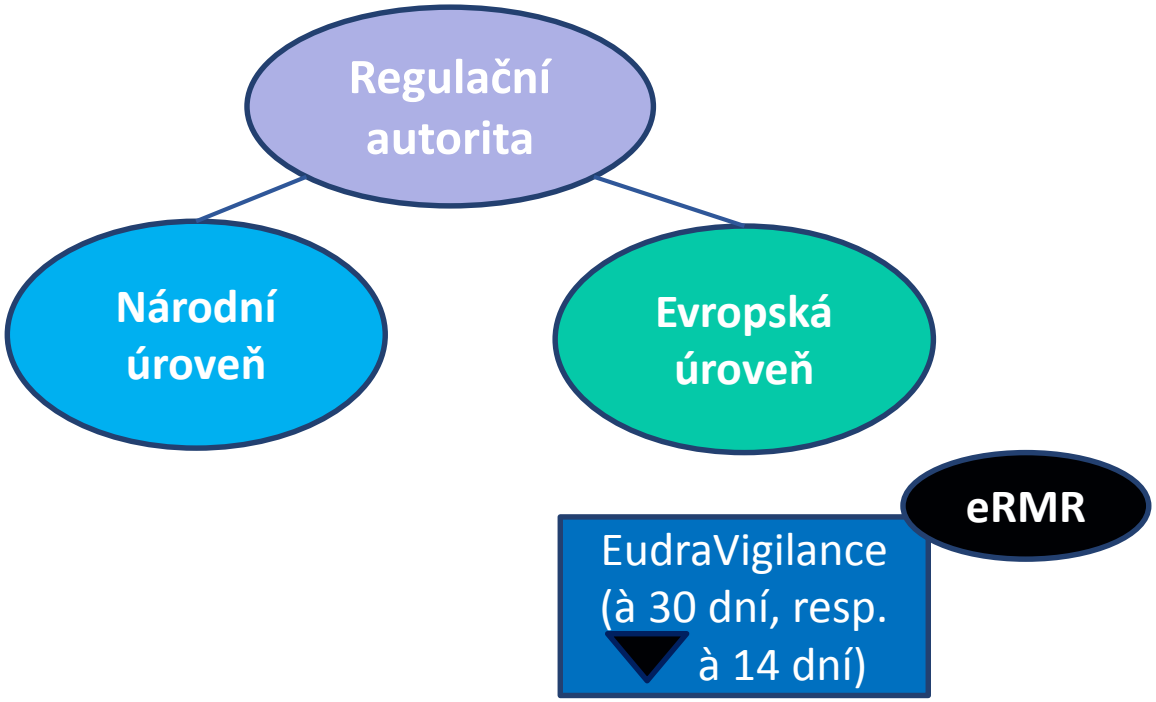
SÚKL

www.sukl.cz/leciva/doporuceni-prac-k-farmakovigilancnim-signalum-2017

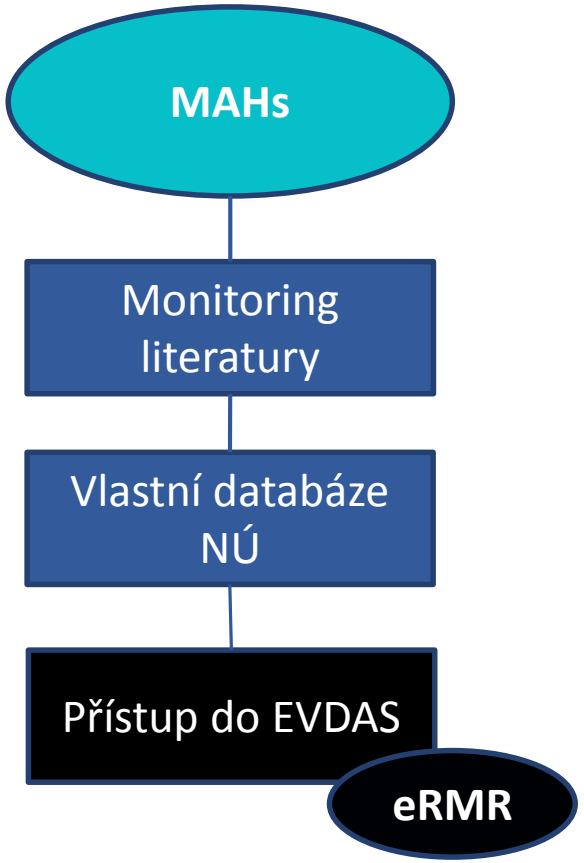
EMA

www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp

Novinky v managementu FV signálů



CAPs – EMA / PRAC Rapp
NAPs – LMS **(CZ 60 látek)**



Aktuální přehled lead member states

List of substances and products subject to worksharing for signal management

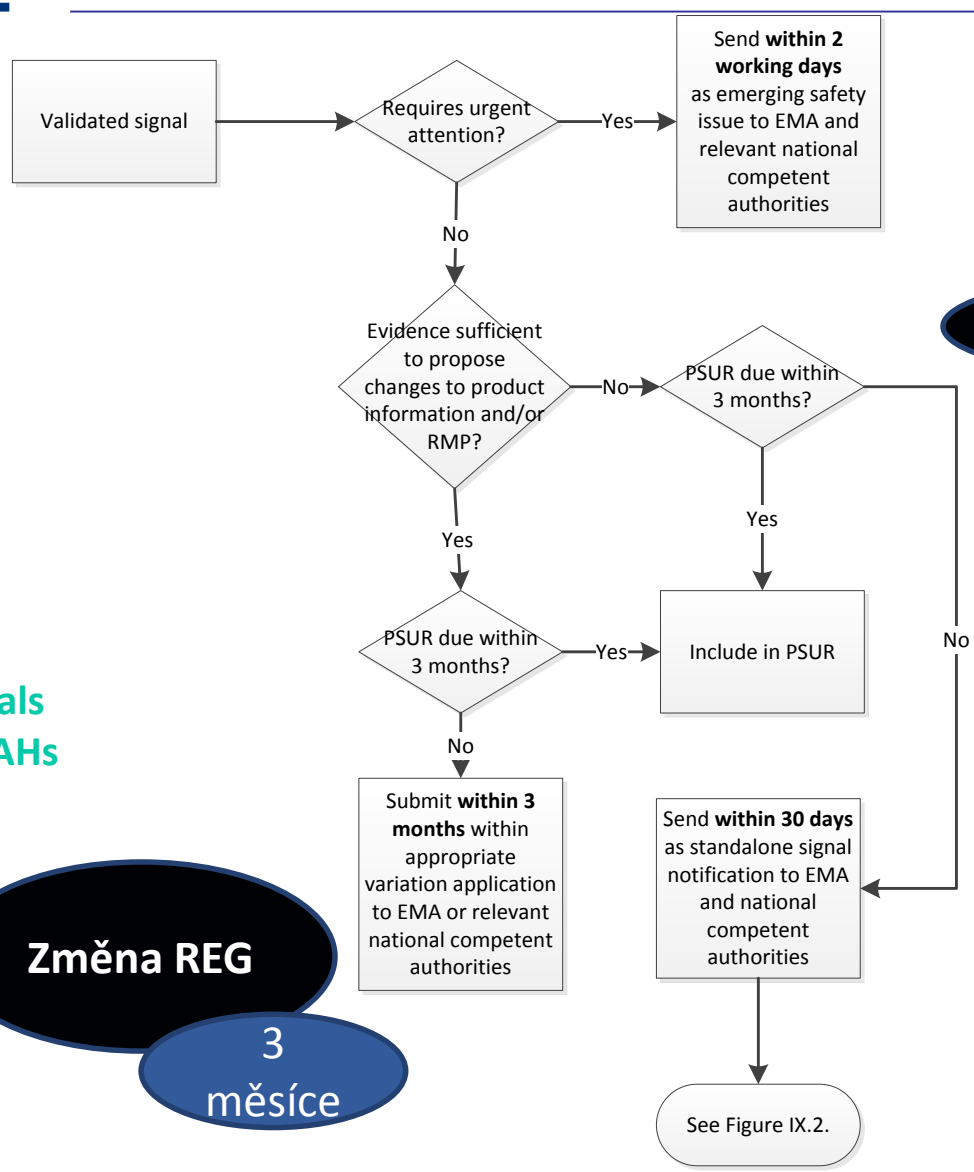
aktualizace duben 2017

www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=worksharing+for+signal+management&mid=WC0b01ac0580727d1b

List of substances and products subject to worksharing for signal management

	A	B
23	Active substance(s) / product name(s)	Lead Member Stat
39	acetic acid glacial / calcium chloride dihydrate / glucose monohydrate / magnesium chloride hexahydrate / potassium chloride / sodium chloride / sodium dihydrogen phosphate dihydrate / sodium hydrogen carbonate	Czech Republic
94	alprostadil	Czech Republic
127	amlodipine / candesartan	Czech Republic
252	benzododecinium bromide	Czech Republic
297	bismuth subgallate / charcoal activated / citric acid	Czech Republic
307	boric acid / carbethopendecinium bromide / sodium tetraborate	Czech Republic
314	bromelain	Czech Republic
319	brompheniramine	Czech Republic
342	caffeine / paracetamol	Czech Republic
372	carbaethopendecinium	Czech Republic
373	carbaethopendecinium bromide / trimecaine hydrochloride	Czech Republic
383	carboprost	Czech Republic
398	cefixime	Czech Republic
422	cetylpyridinium	Czech Republic
425	charcoal activated / sodium thiosulfate	Czech Republic
427	chlorambucil	Czech Republic
429	chloramphenicol	Czech Republic

IX. Appendix 1
Figure IX.1
Notifications and procedural options for **signals validated by MAHs**



ESI (GVP VI) 2 dny

P-PV-emerging-safety-issue@ema.europa.eu

PSUR (GVP VII) 3 měsíce

Notifikace do EMA a NCAs 30 dní

Změna REG 3 měsíce

Nové materiály týkající se EudraVigilance a EVDAS

Screening for adverse reactions in EudraVigilance

prosinec 2016

www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf

EVDAS training for Marketing Authorisation Holders

leden 2017

www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500219435

www.youtube.com/watch?v=TD-wbHiAMx4

EVDAS training for Marketing Authorisation Holders

EUROPEAN MEDICINES AGENCY

Screening for adverse reactions in EudraVigilance

The tools used for signal detection in EudraVigilance are outputs from EVDAS

- The eRMR
- The line listing
- The ICSR Form

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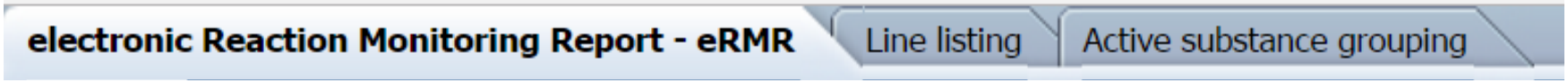
eRMR – electronic Reaction Monitoring Report

- agregovaná data z EV, která lze využít pro detekci signálů a průběžný monitoring jednotlivých látek

- **Pro NCAs** produkuje EMA s periodou 14 dní až 6 měsíců – medicínsky a/nebo statisticky významné jevy jsou označeny prioritou
- **Pro MAHs** přístup prostřednictvím EVDAS, 1. rok pouze pro látky pod additional monitoring – finálně rozhodne EK



Příklad eRMR

Active Substance	SOCs	HLGTs	HLTs	SMQ Broad	SMQ Narrow	PTs	New EVPM	Total EVPM	IME/DME	New Fatal	Total Fatal	New Medication Error/Abuse	Total Medication Error/Abuse	New Paediatric	Total Paediatric	New Geriatric	Total Geriatric	New EEA	Total EEA	New Health Care Professional	Total Health Care Professional	New Serious	Total Serious	New Spontaneous	Total Spontaneous	ROR (-)	ROR	SDR	Changes	New Literature	Total Literature	New Observatic
	Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestinal haemorrhages			Gastrointestinal haemorrhage	0	1	IME	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0.28	2.05	No		0	0	
	Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestinal haemorrhages			Haematochezia	0	1	IME	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0.91	6.67	No		0	0	
	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Colitis (excl infective)			Colitis	0	1		0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1.24	9.12	No		0	0	
	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Oesophagitis (excl infective)			Oesophagitis	0	1		0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	2.25	17.11	No		0	0	
	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (excl infective)			Diarrhoea	0	7		0	1	0	0	0	0	0	0	0	7	0	0	0	7	0	4	1.18	2.53	Yes		0	0	
	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Gastrointestinal atonic and hypomotility disorders NEC			Constipation	0	1		0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0.22	1.59	No		0	0	
	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)			Abdominal pain	0	4		0	1	0	0	0	0	0	0	0	4	0	0	0	4	0	3	0.90	2.45	No		0	0	
	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms			Nausea	0	13		0	1	0	0	0	0	0	1	0	12	0	2	0	12	0	8	1.54	2.73	Yes		0	0	
	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms			Retching	0	1		0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	1.20	8.83	No		0	0	
	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms			Vomiting	0	13		0	1	0	0	0	0	0	2	0	12	0	1	0	13	0	7	2.37	4.21	Yes		0	0	
	Gastrointestinal disorders	Gastrointestinal ulceration and perforation	Gastric ulcers and perforation			Gastric ulcer	0	1	IME	0	1	0	0	0	0	0	1	0	1	0	0	0	1	0	1	0.83	6.08	No		0	0	
	Gastrointestinal disorders	Oral soft tissue conditions	Stomatitis and ulceration			Stomatitis	0	1		0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1.67	12.44	No		0	0	

eRMR pro NCAs

- Priorita 1 – **Designated Medical Events** (DME)
- Priorita 2 – **Important Medical Events** (IME) s **disproporcionalitou** (SDR)
- Priorita 3 – ostatní **fatální případy** s Important Medical Events (IME)

DME

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

Inclusion/exclusion criteria for the IME list

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/08/WC500212100.pdf

Designated Medical Events

Významná mortalita a vysoce pravděpodobná souvislost s podaním LP

Designated Medical Event (DME) List		
Acute hepatic failure	Dermatitis exfoliative generalised	Pancreatitis acute
Acute kidney injury	Drug reaction with eosinophilia and systemic symptoms	Pancytopenia
Agranulocytosis	Drug-induced liver injury	Product contamination microbial
Anaphylactic reaction	Erythema multiforme	Progressive multifocal leukoencephalopathy
Anaphylactic shock	Febrile neutropenia	Pulmonary arterial hypertension
Anaphylactoid reaction	Granulocytopenia	Pulmonary fibrosis
Anaphylactoid shock	Haemolysis	Pulmonary hypertension
Angioedema	Haemolytic anaemia	Renal failure
Aplasia pure red cell	Hepatic failure	Reye's syndrome
Aplastic anaemia	Hepatic infarction	Rhabdomyolysis
Autoimmune haemolytic anaemia	Hepatic necrosis	Stevens-Johnson syndrome
Autoimmune hepatitis	Hepatitis fulminant	Sudden cardiac death
Autoimmune pancreatitis	Immune thrombocytopenic purpura	Sudden hearing loss
Azotaemia	Intestinal perforation	Sudden visual loss
Blindness	Ischaemic pancreatitis	Thrombotic thrombocytopenic purpura
Bone marrow failure	Neutropenic colitis	Torsade de pointes
Deafness	Neutropenic infection	Toxic epidermal necrolysis
Deafness neurosensory	Neutropenic sepsis	Toxic optic neuropathy
Deafness permanent	Oedematous pancreatitis	Transmission of an infectious agent via product
Deafness transitory	Optic ischaemic neuropathy	Ventricular fibrillation
Dermatitis exfoliative	Pancreatitis	

Disproporcionalita v eRMR:
ROR – Reporting odds ratio

Calculation of the ROR

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- The calculation of the ROR is based on a two-by-two contingency table

	Event	Not Event
Medicinal product	a	b
Not product	c	d

$$ROR = \frac{a/b}{c/d}$$

- The 95% confidence interval of the ROR is also computed in the eRMR

a	Number of individual cases with the suspected medicinal product and the adverse event
b	Number of individual cases with the suspected medicinal product but not event of interest
c	Number of individual cases with the event of interest but not the medicinal product of interest
d	Number of individual cases with no event of interest or medicinal product of interest

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Disproporcionalita v eRMR:
SDR - Signal of Disproportionate Reporting

- ROR(-) ≥1
- Important Medical Events (IME)
- minimálně 3 případy u látek pod additional monitoring (kromě PASS)/ minimálně 5 případů u ostatních látek

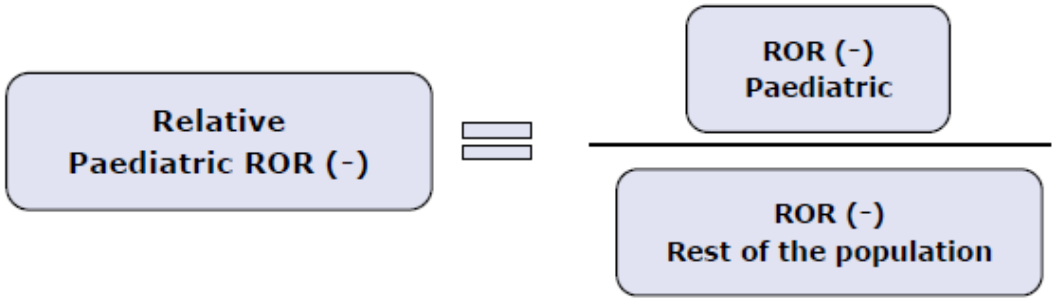
- Disproporcionalita dle místa výskytu

New Spontaneous	Tot Sp. Europe	Tot Sp. North America	Tot Sp. Japan	Tot Sp. Asia	Tot Sp. Rest	Tot Spontaneous	ROR (-) Europe	ROR (-) North America	ROR (-) Japan	ROR (-) Asia	ROR (-) Rest	ROR (-) All

SDR pro speciální populace

Disproporcionalita v eRMR je počítaná zvlášť pro speciální populace – pediatrické pacienty a seniory

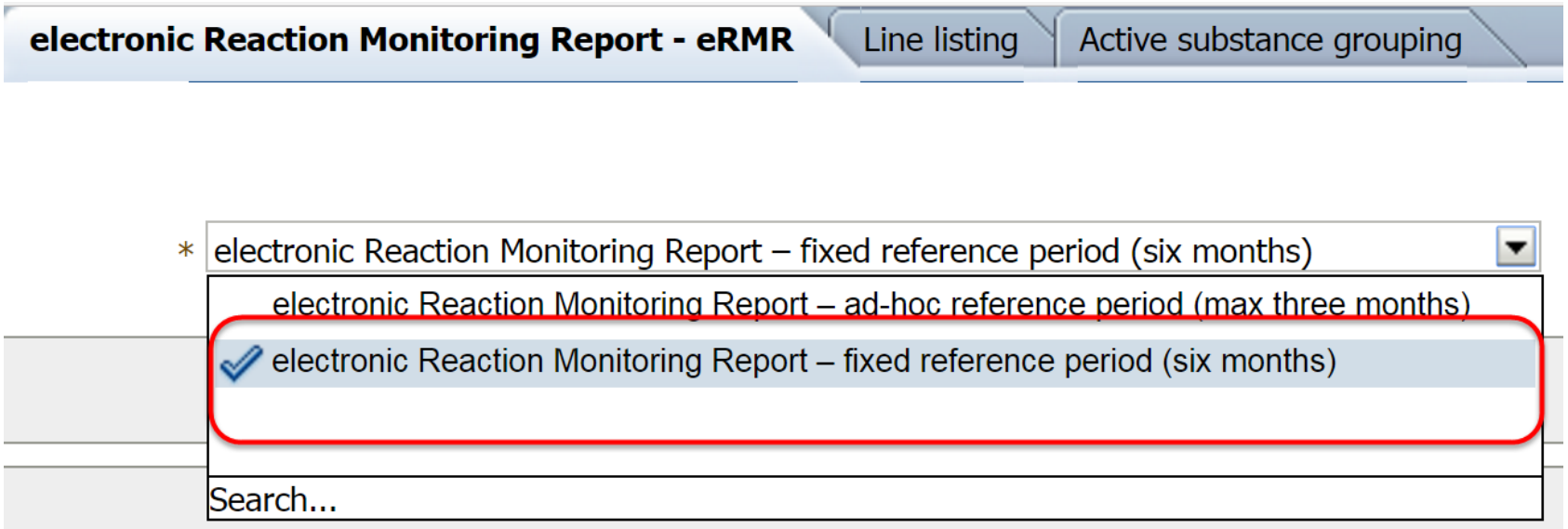
New Paed	Tot Paed	Ratio ROR (-) Paed vs Others	Paediatric SDR
2	5	3.26	Yes

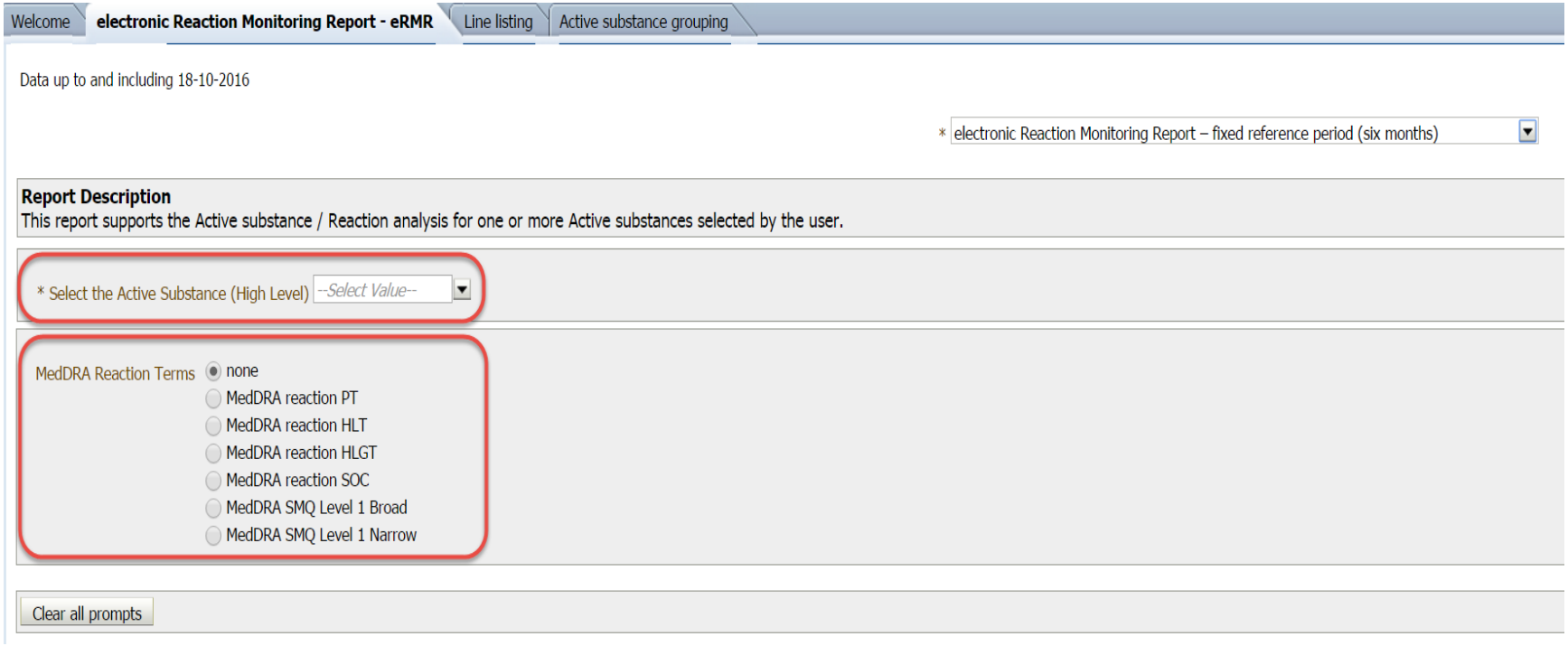


Možnosti eRMR reportů v EVDAS

fixní perioda

produkce 1. den v měsíci – EMA, referenční perioda bude nastavena na 6 měsíců

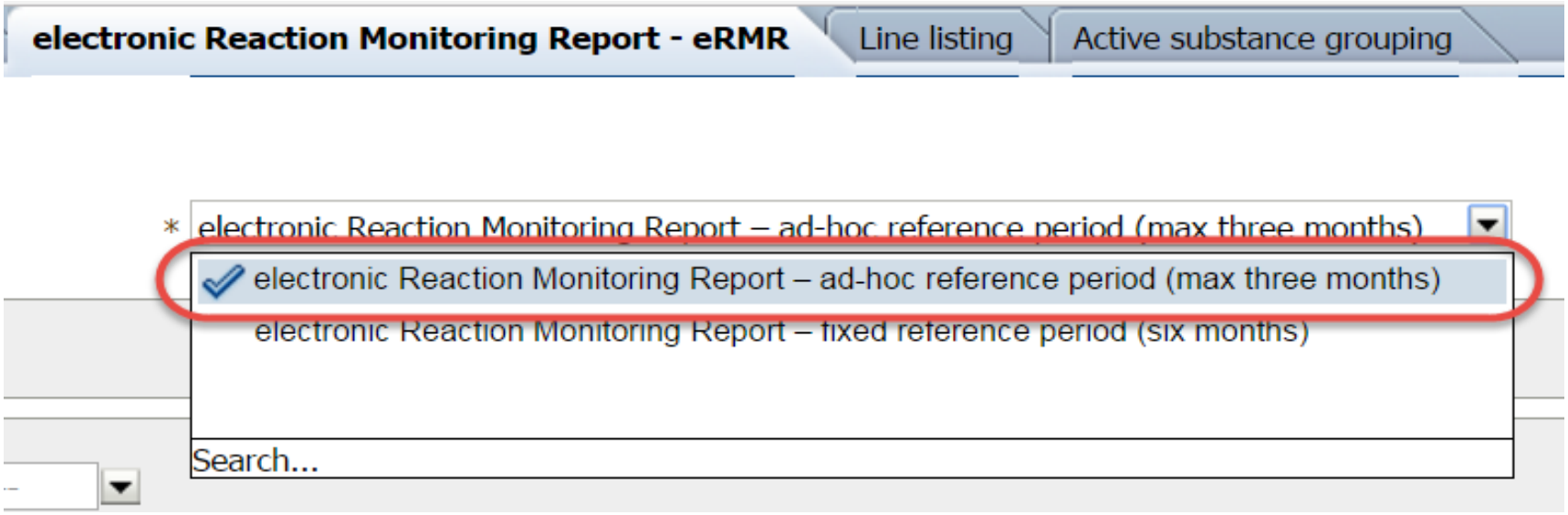


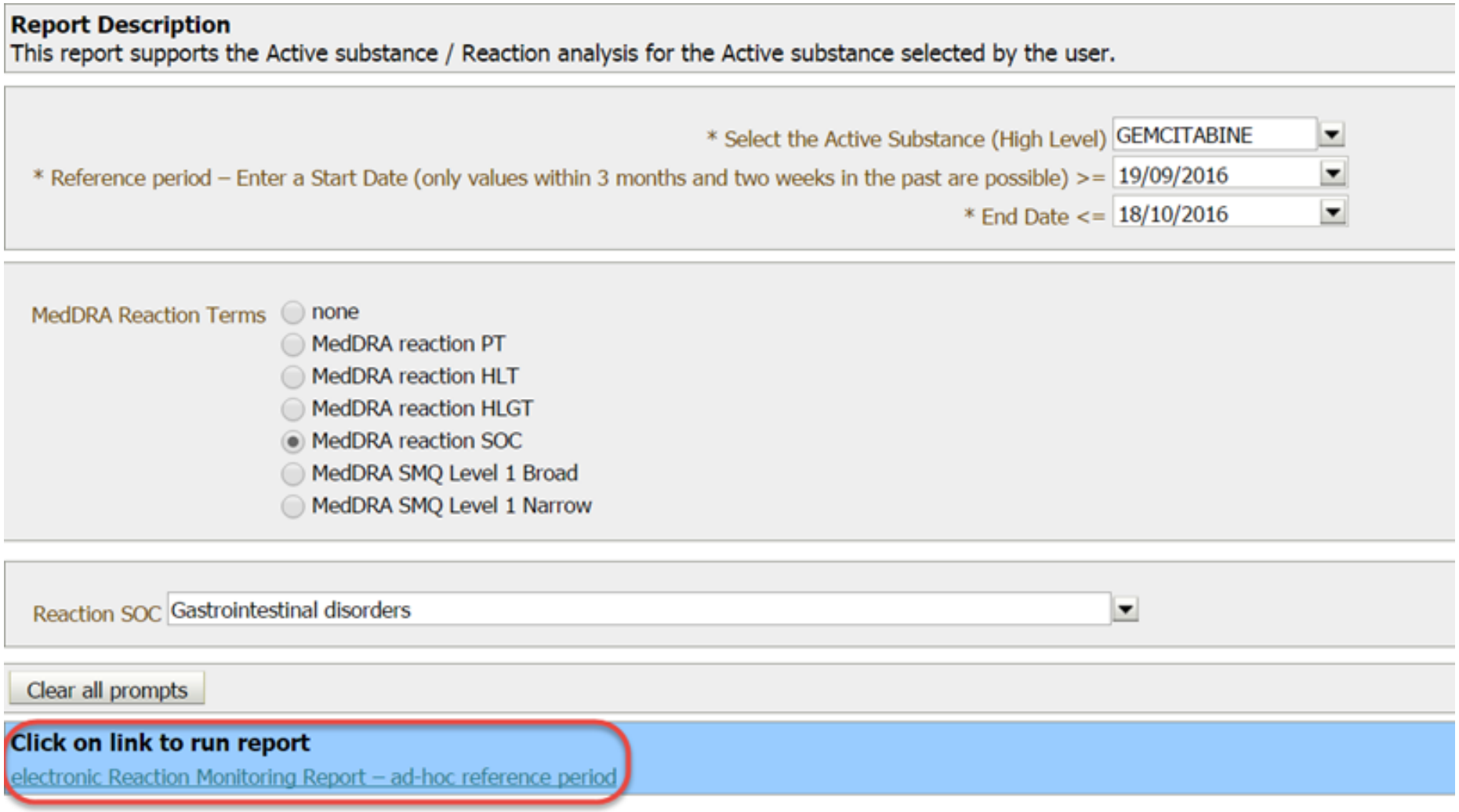


Možnosti eRMR reportů v EVDAS

ad-hoc referenční perioda

lze zobrazit data za poslední 3 měsíce a 2 týdny, tedy max. 105 uplynulých dní





Report Description
This report supports the Active substance / Reaction analysis for the Active substance selected by the user.

* Select the Active Substance (High Level) GEMCITABINE

* Reference period – Enter a Start Date (only values within 3 months and two weeks in the past are possible) >= 19/09/2016

* End Date <= 18/10/2016

MedDRA Reaction Terms
- none
- MedDRA reaction PT
- MedDRA reaction HLT
- MedDRA reaction HLGT
- MedDRA reaction SOC
- MedDRA SMQ Level 1 Broad
- MedDRA SMQ Level 1 Narrow

Reaction SOC Gastrointestinal disorders

Clear all prompts

Click on link to run report
electronic Reaction Monitoring Report – ad-hoc reference period

New EVPM	Total EVPM	New EEA	Tot EEA	New HCP	Tot HCP	New Serious	Tot Serious	New Obs	Tot Obs	New Fatal	Tot Fatal	New Med Err	Tot Me Err	New + RC	Tot + RC	New Lit	Tot Lit
0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
0	2	0	2	0	2	0	2	0	0	0	2	0	0	0	0	0	0
0	1	0	1	0	1	0	1	0	0	0	1	0	0	0	**0**	0	0
0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0

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eRMR – obecné informace

- eRMR lze zobrazit pouze pro 1 substanci současně
- Reporty lze exportovat (pdf, excel...) i uložit do „oblíbených“ pro opakované hledání
- Manuál pro MAHy: EV-G1a - MAH's level 1 access via EVDAS (Q4 2017)
- Report obsahuje prokliky na **line listing**

EU Local Number	Worldwide Unique Case Identification	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference
EU-EC-10568426	CZ-EMA-20160420-ashishvp-171022185	21/04/2016	Spontaneous	Healthcare professional (Physician)	EEA	Svojgr K, Sumerauer D, Puchmajerova A, Vicha A, Hrusak O, Michalova K et al. Fanconi anemia with biallelic FANCD1/BRCA2 mutations - Case report of a family with three affected children.European Journal of Medical Genetics. 2016; 59(3):152-157

Patient Age Group	Patient Age Group (as per reporter)	Patient Sex	Parent Child Report
18-64 Years	Adult	Male	No

Reaction List PT (Duration – Outcome - Seriousness Criteria)	Suspect/interacting Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])	Concomitant/Not Administered Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])
Nausea (n/a - Not Recovered/Not Resolved - Caused/Prolonged Hospitalisation) Vomiting (n/a - Not Recovered/Not Resolved - Caused/Prolonged Hospitalisation)	[MERCAPTOPURINE MONOHYDRATE] (S - Autoimmune hepatitis - Drug withdrawn - [n/a - n/a - Not available])	[SULFAMETHOXAZOLE, TRIMETHOPRIM] (C - Prophylaxis - Unknown - [n/a - 140mg - ORAL])

eRMR - shrnutí

- Designated medical events
- Important medical events s disproporcionalitou
- Disproporcionalita u vulnerabilních populací
- Jiné fatální případy s IME

Děkuji za pozornost

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