

## Online Resources 1-7

**Article title:** Use and safety of anthroposophic medicinal products, An analysis of 44,662 patients from the EvaMed Pharmacovigilance Network

**Author names:** Harald Johan Hamre, Anja Glockmann, Kirsten Heckenbach, Harald Matthes

**Affiliation and e-mail address of the corresponding author:** Harald Johan Hamre, Institute for Applied Epistemology and Medical Methodology at the University of Witten/Herdecke, [harald.hamre@ifaemm.de](mailto:harald.hamre@ifaemm.de)

## Online Resource 1 Categories and criteria for causality assessment of adverse events and drugs. Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Causality term	Assessment criteria (all points should be reasonably complied with)
Certain	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with plausible time relationship to drug intake</li> <li>• Cannot be explained by disease or other drugs</li> <li>• Response to withdrawal plausible (pharmacologically, pathologically)</li> <li>• Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)</li> <li>• Rechallenge satisfactory, if necessary</li> </ul>
Probable / Likely	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with reasonable time relationship to drug intake</li> <li>• Unlikely to be attributed to disease or other drugs</li> <li>• Response to withdrawal clinically reasonable</li> <li>• Rechallenge not required</li> </ul>
Possible	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with reasonable time relationship to drug intake</li> <li>• Could also be explained by disease or other drugs</li> <li>• Information on drug withdrawal may be lacking or unclear</li> </ul>
Unlikely	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)</li> <li>• Disease or other drugs provide plausible explanations</li> </ul>
Conditional / Unclassified	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality</li> <li>• More data for proper assessment needed, or</li> <li>• Additional data under examination</li> </ul>
Unassessable / Unclassifiable	<ul style="list-style-type: none"> <li>• Report suggesting an adverse reaction</li> <li>• Cannot be judged because information is insufficient or contradictory</li> <li>• Data cannot be supplemented or verified</li> </ul>

*Cited from: The use of the WHO-UMC system for standardised case causality assessment. Uppsala Monitoring Centre (accessed 28 August 2017).*

**Online Resource 2 List of adverse drug reactions to anthroposophic medicinal products**

Patient		Adverse drug reaction					Symptom 1		Symptom 2		Symptoms 3-5
Sex	Age y	Dura- tion d	Inten- sity	Mana- gement	Out- come	MedDRA Code	Text	MedDRA Code	Text	<i>A-M listed underneath</i>	
f	51	103	II	3	1	10000060	Flatulence, bloating and distension				
f	57	ND	II	1	1	10000087	Gastrointestinal and abdominal pains (excl oral and throat)				
m	11	4	I	1	1	10000087	Gastrointestinal and abdominal pains (excl oral and throat)				
f	51	17	II	1	1	10000133	Faecal abnormalities NEC				
m	12	23	II	1	1	10001488	Behaviour and socialisation disturbances				
f	86	16	I	1	1	10001488	Behaviour and socialisation disturbances				
f	1	5	I	1	1	10001488	Behaviour and socialisation disturbances				
m	2	1	I	1	1	10001497	Anxiety symptoms				
f	63	59	II	1	1	10001854	Disturbances in consciousness NEC				
f	65	6	II	2	1	10003041	Application and instillation site reactions				
f	51	7	I	1	1	10003246	Arthropathies NEC				
f	74	ND	II	3	2	10005034	Bladder and urethral symptoms				
m	29	1	II	1	1	10005148	Lid, lash and lacrimal infections, irritations and inflammations	10010725	Conjunctival infections, irritations and inflammations		
f	67	1	I	1	1	10006789	Paraesthesias and dysaesthesias				
f	50	5	I	4	1	10008469	Pain and discomfort NEC				
f	2	4	II	1	1	10010774	Gastrointestinal atonic and hypomotility disorders NEC				
m	8	2	I	1	2	10011224	Coughing and associated symptoms				
f	46	43	II	1	1	10012378	Depressive disorders	10016256	Asthenic conditions		
f	54	1	II	1	1	10012735	Diarrhoea (excl infective)	10033557	Cardiac signs and symptoms NEC	A	
f	84	85	I	1	1	10012735	Diarrhoea (excl infective)	10036018	Bladder and urethral symptoms		
f	72	46	III	2	1	10013573	Neurological signs and symptoms NEC	10061224	Musculoskeletal and connective tissue pain and discomfort	B	

f	92	1	II	1	1	10013573	Neurological signs and symptoms NEC	10020772	Vascular hypertensive disorders NEC	
f	2	9	II	1	1	10013687	Dermatitis ascribed to specific agent			
m	2	3	I	1	1	10013687	Dermatitis ascribed to specific agent			
f	2	2	II	1	1	10013687	Dermatitis ascribed to specific agent			
f	55	44	I	1	1	10013781	Oral dryness and saliva altered			
f	40	3	I	1	1	10013781	Oral dryness and saliva altered			
f	40	3	I	1	1	10013781	Oral dryness and saliva altered			
m	46	2	I	1	1	10013946	Dyspeptic signs and symptoms			
m	4	6	II	1	1	10014184	Dermatitis and eczema			
m	2	1	I	1	1	10014866	Gastrointestinal inflammatory disorders NEC			
f	48	5	II	1	1	10015150	Erythemas	10037087	Pruritus NEC	
m	74	0	I	1	1	10015150	Erythemas	10061218	Inflammations	
ND	5	3	I	1	1	10015958	Ocular disorders NEC			
f	38	6	I	2	1	10016256	Asthenic conditions			
f	47	1	I	1	1	10017999	Gastrointestinal and abdominal pains (excl oral and throat)			
f	36	1	II	3	1	10017999	Gastrointestinal and abdominal pains (excl oral and throat)			
f	36	1	II	2	1	10019211	Headaches NEC	10025482	Asthenic conditions	C,D,E
f	38	7	II	3	1	10020642	Apocrine and eccrine gland disorders	10000496	Acnes	
f	74	0	II	2	1	10020751	Allergic conditions NEC			
f	65	16	I	2	1	10020751	Allergic conditions NEC			
m	1	5	I	1	1	10020751	Allergic conditions NEC	10055182	Dermatitis and eczema	
f	38	2	II	1	1	10020751	Allergic conditions NEC			
f	57	1	III	1	1	10020751	Allergic conditions NEC			
f	71	5	I	1	1	10020751	Allergic conditions NEC			
f	45	0	I	1	1	10020751	Allergic conditions NEC			
f	3	1	III	1	1	10020993	Hypoglycaemic conditions NEC			
f	48	ND	II	2	2	10022035	Disturbances in initiating and maintaining sleep			
m	62	7	III	1	1	10025482	Asthenic conditions	10007649	Cardiac disorders NEC	F,G

f	43	ND	II	1	1	10025482	Asthenic conditions	10061224	Musculoskeletal and connective tissue pain and discomfort	
m	2	5	I	3	1	10028521	Pupil disorders			
f	72	ND	II	1	1	10028740	Nasal disorders NEC	10013781	Oral dryness and saliva altered	
f	9	13	II	1	1	10028813	Nausea and vomiting symptoms			
f	40	19	II	1	1	10029263	Dermatitis and eczema			
m	0	43	II	1	1	10030124	Oedema NEC			
m	37	2	II	1	1	10033557	Cardiac signs and symptoms NEC	10061224	Musculoskeletal and connective tissue pain and discomfort	
f	7	3	III	1	1	10033670	Panic attacks and disorders			
f	2	3	I	1	1	10034545	Ocular disorders NEC			
m	74	41	II	2	2	10037087	Pruritus NEC	10015150	Erythemas	
m	6	4	I	1	1	10037087	Pruritus NEC	10046735	Urticarias	
m	28	15	II	4	1	10037087	Pruritus NEC			
f	53	6	III	2	1	10037660	Febrile disorders	10013968	Breathing abnormalities	H,I
m	8	7	II	1	1	10037844	Rashes, eruptions and exanthems NEC			
f	1	1	I	1	1	10037844	Rashes, eruptions and exanthems NEC			
f	1	4	I	1	1	10037844	Rashes, eruptions and exanthems NEC			
f	55	1	I	3	1	10038687	Breathing abnormalities			
f	45	0	III	1	1	10038687	Breathing abnormalities	10033670	Panic attacks and disorders	J,K
f	73	2	I	1	1	10038743	Increased physical activity levels			
m	55	1	II	2	1	10038743	Increased physical activity levels	10013687	Dermatitis ascribed to specific agent	L
m	3	3	I	1	1	10038743	Increased physical activity levels	10040984	Sleep disorders NEC	
f	30	10	I	3	1	10038743	Increased physical activity levels			
m	2	7	II	1	1	10038743	Increased physical activity levels			
m	3	3	I	2	1	10038743	Increased physical activity levels			
m	1	5	I	1	1	10038743	Increased physical activity levels			
f	0	18	I	1	1	10038743	Increased physical activity levels			
f	1	1	II	1	1	10038743	Increased physical activity levels			
f	3	3	I	1	1	10038743	Increased physical activity levels			

m	3	6	I	1	1	10038743	Increased physical activity levels	10040984	Sleep disorders NEC	
m	0	5	II	1	1	10038743	Increased physical activity levels			
m	1	5	II	1	1	10038743	Increased physical activity levels			
m	1	3	II	1	1	10038743	Increased physical activity levels			
f	0	2	I	1	1	10038743	Increased physical activity levels			
m	10	2	II	1	1	10038743	Increased physical activity levels			
f	77	3	I	1	1	10040849	Dermal and epidermal conditions NEC			
f	44	15	II	1	1	10040893	Dermal and epidermal conditions NEC			
m	9	4	I	1	1	10041232	Upper respiratory tract signs and symptoms			
f	78	12	I	1	1	10042868	Synovial disorders			
f	38	14	I	1	1	10043949	Tongue signs and symptoms	10000059	Gastrointestinal signs and symptoms NEC	M
f	40	27	I	1	1	10044032	Dental surface disorders			
f	44	2	II	4	1	10046735	Urticarias			
f	2	1	II	1	1	10046735	Urticarias			
f	0	1	I	1	1	10046735	Urticarias			
f	1	3	I	1	2	10046735	Urticarias			
m	7	5	II	1	1	10047700	Nausea and vomiting symptoms			
f	50	ND	II	1	1	10049044	Skin structures and soft tissue infections			
f	51	2	I	3	1	10052137	Ear disorders NEC			
f	51	9	I	1	1	10053424	Application and instillation site reactions	10015150	Erythemas	
f	35	2	I	1	1	10061305	Nasal disorders NEC			
m	0	5	I	1	1	10068172	Anal and rectal signs and symptoms	10014184	Dermatitis and eczema	
m	36	5	I	1	1	10074859	Faecal abnormalities NEC	10000059	Gastrointestinal signs and symptoms NEC	

*Intensity: I = Grade I (mild); II = Grade II (moderate); III = Grade III (severe). Outcome: 1 = recovered; 2 = not yet recovered. Management: 1 = drug withdrawal; 2 = dose reduction; 3 = no precautions; 4 = no data. MedDRA: Medical Dictionary for Regulatory Activities. NEC: not elsewhere classified. ND: No data.*

*Symptoms 3-5 in Online Resource 4, consecutively ordered (A-M)*

<b>A-M</b>	<b>MedDRA Code</b>	<b>Text</b>
A	10038687	Breathing abnormalities
B	10021097	Vascular hypotensive disorders
C	10037087	Pruritus NEC
D	10053424	Application and instillation site reactions
E	10015150	Erythemas
F	10000059	Gastrointestinal signs and symptoms NEC
G	10020910	Breathing abnormalities
H	10022000	Influenza viral infections
I	10019211	Headaches NEC
J	10033775	Paraesthesias and dysaesthesias
K	10002855	Anxiety symptoms
L	10007649	Cardiac disorders NEC
M	10016256	Asthenic conditions

**Online Resource 3 Indications for prescriptions of anthroposophic vs. non-anthroposophic medicinal products in adults, most frequent diagnosis chapters of the International Classification of Diseases, Tenth Revision**

Chapter	Code	Text	AMPs		Non-AMPs	
			N	Percent	N	Percent
XIII	M00–M99	Diseases of the musculoskeletal system and connective tissue	13,404	11.6%	17,250	10.8%
X	J00–J99	Diseases of the respiratory system	13,314	11.6%	14,681	9.2%
II	C00–D48	Neoplasms	12,703	11.0%	13,827	8.6%
IX	I00–I99	Diseases of the circulatory system	11,904	10.3%	25,408	15.8%
V	F00–F99	Mental and behavioural disorders	9,749	8.5%	13,047	8.1%
IV	E00–E90	Endocrine, nutritional and metabolic diseases	8,943	7.8%	18,484	11.5%
XI	K00–K93	Diseases of the digestive system	7,867	6.8%	10,856	6.8%
XVIII	R00–R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	6,414	5.6%	7,704	4.8%
XII	L00–L99	Diseases of the skin and subcutaneous tissue	6,021	5.2%	7,015	4.4%
Other chapters (with <5% in each group)			24,738	21.5%	32,050	20.0%
Total evaluable diagnoses			115,057	100.0%	160,322	100.0%

*AMPs: Anthroposophic medicinal products. Non-AMPs: all other medicinal products.*



**Online Resource 4 Indications for prescriptions of anthroposophic vs. non-anthroposophic medicinal products in children, most frequent diagnosis chapters of the International Classification of Diseases, Tenth Revision**

Chapter	Code	Text	AMPs		Non-AMPs	
			N	Percent	N	Percent
X	J00–J99	Diseases of the respiratory system	61,127	32.4%	74,714	31.4%
I	A00–B99	Certain infectious and parasitic diseases	18,689	9.9%	31,078	13.1%
XVIII	R00–R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	18,485	9.8%	24,343	10.2%
XXI	Z00–Z99	Factors influencing health status and contact with health services	14,795	7.8%	18,798	7.9%
XII	L00–L99	Diseases of the skin and subcutaneous tissue	13,622	7.2%	17,004	7.2%
VIII	H60–H95	Diseases of the ear and mastoid process	11,601	6.1%	11,350	4.8%
XI	K00–K93	Diseases of the digestive system	10,080	5.3%	15,057	6.3%
Other chapters (with <5% in each group)			40,269	21.3%	45,429	19.1%
Total evaluable diagnoses			188,668	100.0%	237,773	100.0%

*AMPs: Anthroposophic medicinal products. Non-AMPs: all other medicinal products.*

### Online Resource 5 Features of adverse drug reactions to anthroposophic medicinal products vs. all other medicinal products, respectively. Patients of all physicians

Item	ADR to AMPs (n = 100)		ADR to Non-AMPs (n = 682)		P-value
	N	Percent	N	Percent	
<b>Serious ADR</b>	1/100	1.0%	29/682	4.3%	0.1609*
<b>Severity of ADR</b>					0.0000**
Grade I	50/100	50.0%	139/680	20.4%	
Grade II	43/100	43.0%	459/680	67.5%	
Grade III	7/100	7.0%	78/680	11.5%	
Grade IV	0/100	0.0%	4/680	0.6%	
<b>Number of symptoms per ADR</b>					0.1056**
1	74/100	74.0%	551/682	80.8%	
2	18/100	18.0%	97/682	14.2%	
≥3	8/100	8.0%	34/682	5.0%	
<b>Occurrence of ADR</b>					0.0000**
Once	17/100	17.0%	60/671	8.9%	
Several times	40/100	40.0%	78/671	11.6%	
Continuous	43/100	43.0%	533/671	79.4%	
<b>Duration of ADR</b>					0.1341**
<24h	4/94	4.3%	32/639	5.0%	
1-2 days	28/94	29.8%	194/639	30.4%	
3-6 days	34/94	36.2%	291/639	45.5%	
7-13 days	10/94	10.6%	58/639	9.1%	
≥14 days	18/94	19.1%	64/639	10.0%	
<b>Management of ADR</b>					0.0000**
Drug withdrawal	78/97	80.4%	351/621	56.5%	
Dose reduction	11/97	11.3%	12/621	1.9%	
No precautions	8/97	8.2%	258/621	41.5%	
<b>Outcome of ADR</b>					0.5289*
Recovered	95/100	95.0%	618/666	92.8%	
Not yet recovered	5/100	5.0%	48/666	7.2%	

The analyses reflect the relative frequency of ADR features within each MP group (not the absolute frequencies) and are based on the ADRs with evaluable data for the respective feature. AMPs: Anthroposophic medicinal products. Non-AMPs: all other medicinal products. \*Fisher's Exact Test. \*\*Mann-Whitney U Test.

**Online Resource 6 Frequency of adverse drug reactions to anthroposophic medicinal products in relation to prescriptions in patients with respiratory and ear infections (ICD-10 H66-H67, H70, H72, J00, J02-J06, J20, J40): patients of prescriber physicians in EvaMed vs. the AM Group of IIPCOS**

<b>Study</b>	<b>EvaMed (this study)</b>	<b>IIPCOS, AM Group</b>
Confirmed ADRs to AMPs, all Grades	23	2
Patients with confirmed ADR	23	2
Patients with prescriptions	6,743	715
Patients with ADRs to AMPs / with prescriptions	0.34%	0.28%

*AMPs: Anthroposophic medicinal products. Non-AMPs: all other medicinal products. ADRs: Adverse drug reactions. EvaMed: Evaluation of Anthroposophic Medicine. IIPCOS, AM Group: International Integrative Primary Care Outcomes Study, patients treated by physicians offering anthroposophic treatment.*

**Online Resource 7 Adverse drug reactions to anthroposophic medicinal products in adult patients of prescriber physicians in EvaMed vs. AMOS patients enrolled 1 Jan 1999 to 31 March 2001\*, samples restricted for age group (18-75 years)\*\* and ICD-10 Diagnosis Blocks\*\*\***

Study	EvaMed (this study)	AMOS
Patients with confirmed ADRs to AMPs	20	13
Patients using AMPs	2,900	422
Proportion of AMP users with confirmed ADRs to AMPs	0.69%	3.08%

*EvaMed: Evaluation of Anthroposophic Medicine. AMOS: Anthroposophic Medicine Outcomes Study. ADRs: Adverse drug reactions. AMPs: Anthroposophic medicinal products.*

*\*AMOS patients enrolled 1 Jan 1999 to 31 March 2001: For AMOS patients enrolled 1 April 2001 and later, reports of suspected ADRs were not subject to detailed causality assessment; hence these patients were not included in the present comparison.*

*\*\*Age group: AMOS had an upper age limit of 75 years, EvaMed had no upper age limit. Therefore both samples were restricted to patients aged 18-75 years.*

*\*\*\*ICD-10 Diagnosis Blocks: EvaMed comprised patients with any diagnosis, AMOS comprised patients with any chronic condition. The AMOS sample was restricted to ICD-10 Diagnosis Blocks with at least 5 Patients (83.8% of the sample, n=422/501 patients, 21 Diagnosis Blocks), the EvaMed sample was restricted to the same 21 Diagnosis Blocks: C00-C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue; D10-D36 Benign neoplasms; D80-D89 Certain disorders involving the immune mechanism; E00-E07 Disorders of thyroid gland; F30-F39 Mood [affective] disorders; F40-F48 Neurotic, stress-related and somatoform disorders; G35-G37 Demyelinating diseases of the central nervous system; G40-G47 Episodic and paroxysmal disorders; G90-G99 Other disorders of the nervous system; I10-I15 Hypertensive diseases; I30-I52 Other forms of heart disease; J30-J39 Other diseases of upper respiratory tract; J40-J47 Chronic lower respiratory diseases; K20-K31 Diseases of oesophagus, stomach and duodenum; K50-K52 Noninfective enteritis and colitis; L20-L30 Dermatitis and eczema; M00-M25 Arthropathies; M40-M54 Dorsopathies; M60-M79 Soft tissue disorders; N80-N98 Noninflammatory disorders of female genital tract; R50-R69 General symptoms and signs.*