Supplementary material 2

for

Nanomedicinal products: a survey on specific toxicity and side effects

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Lareb information

The Netherlands Pharmacovigilance Centre Lareb, which collects and analyses spontaneous reports of suspected adverse reactions of medicines, searched for case reports on five sets of drugs. It should be noted that a report in the Lareb database does not necessarily imply a causal relationship between the complaint and the medicine. It should be regarded as a suspicion of the reporter that the medicine might be involved in the complaints. Additionally, due to the nature of spontaneous reporting, no incidence rates can be calculated, and comparisons between drugs should be made with much caution. Still, these data could provide more insight with respect to the nature and severity of the side effects in addition to the frequency reported by the EMA, the Dutch pharmaco-therapeutic compendium and the summaries of product characteristics.

1. Comparison of side effects between Abraxane® and Taxol®

System/Organ Class (SOC) name	Abraxane®		Taxol®		summation	
	n	*%*	*n*	*%*	*n*	*%*
Blood and lymphatic system disorders	8	11.8	58	9.7	66	9.9
Cardiac disorders	1	1.5	24	4.0	25	3.7
Ear and labyrinth disorders	0	0.0	5	0.8	5	0.7
Eye disorders	1	1.5	5	0.8	6	0.9
Gastrointestinal disorders	10	14.7	66	11.0	76	11.4

General disorders and administration site conditions	7	10.3	108	18.0	115	17.2
Hepatobiliary disorders[1]	4	5.9	1	0.2	5	0.7
Immune system disorders	3	4.4	36	6.0	39	5.8
Infections and infestations	0	0.0	26	4.3	26	3.9
Injury, poisoning and procedural complications	2	2.9	15	2.5	17	2.5
Investigations[2]	9	13.2	36	6.0	45	6.7
Metabolism and nutrition disorders	2	2.9	12	2.0	14	2.1
Musculoskeletal and connective tissue disorders	0	0.0	25	4.2	25	3.7
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)[3]	8	11.8	3	0.5	11	1.6
Nervous system disorders	6	8.8	35	5.8	41	6.1
Pregnancy, puerperium and perinatal conditions	0	0.0	3	0.5	3	0.4
Psychiatric disorders	2	2.9	7	1.2	9	1.3
Renal and urinary disorders	0	0.0	7	1.2	7	1.0
Respiratory, thoracic and mediastinal disorders	1	1.5	47	7.8	48	7.2
Skin and subcutaneous tissue disorders	1	1.5	47	7.8	48	7.2
Surgical and medical procedures	0	0.0	2	0.3	2	0.3
Vascular disorders	3	4.4	33	5.5	36	5.4
Total	68	100.0	601	100.0	669	100.0

[1] Hepatobiliary disorders

The side effects mentioned for Abraxane® (each n=1): biliary stricture, biliary disorder (not otherwise specified), cholecystitis, liver disorder (not otherwise specified). The reports are not very well documented.

[2] Investigations

Although there is a difference in percentages, the absolute numbers are very low. The following side effects are listed for Abraxane® more than once: reduced hemoglobin (n=3); decreased neutrophils (n=3). These are known side effects of various chemotherapeutic agents.

[3] Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

The difference in reporting between the two drugs is caused by five reports of pancreatic cancer for Abraxane®. Although reported as side effect, Abraxane® was in fact prescribed for pancreatic cancer and this is probably a progressive disease. The reporting of a disease as side effect stems from the obligation for manufacturers to report such cases, because it may indicate lack of effectiveness of the drug. However, disease progression eventually occurs in most patients, so this may not be regarded as a “real side effect”.

2. Comparison of side effects between AmBisome® and Fungizone® [1]

System/Organ Class (SOC) name	AmBisome®		Fungizone®		summation	
	n	*%*	*n*	*%*	*n*	*%*
Cardiac disorders	2	5.3	7	15.6	9	10.8
Endocrine disorders	0	0.0	1	2.2	1	1.2
Gastrointestinal disorders	2	5.3	4	8.9	6	7.2
General disorders and administration site conditions[2]	15	39.5	6	13.3	21	25.3
Hepatobiliary disorders	0	0.0	1	2.2	1	1.2
Infections and infestations	1	2.6	2	4.4	3	3.6
Injury, poisoning and procedural complications	4	10.5	7	15.6	11	13.3
Investigations	1	2.6	2	4.4	3	3.6
Metabolism and nutrition disorders	5	13.2	5	11.1	10	12.1
Musculoskeletal and connective tissue disorders	2	5.3	1	2.2	3	3.6
Nervous system disorders	1	2.6	2	4.4	3	3.6
Renal and urinary disorders[3]	0	0.0	1	2.2	1	1.2
Respiratory, thoracic and mediastinal disorders	2	5.3	2	4.4	4	4.8
Skin and subcutaneous tissue disorders	0	0.0	3	6.7	3	3.6
Surgical and medical procedures	1	2.6	0	0.0	1	1.2
Vascular disorders	2	5.3	1	2.2	3	3.6
Total	38	100.0	45	100.0	83	100.0

[1] Note that Fungizone® is available for both oral as well as intravenous administration

[2] General disorders and administration site conditions

The number of reports for this SOC is considerably higher for AmBisome® than for Fungizone®. The absolute numbers are, however, quite small. The difference in reporting is mainly because a relatively large number of reports were received for AmBisome® on its lack of effectiveness. It should be noted that all these reports were received from the Marketing Authorization Holder of AmBisome®; the Marketing Authorization Holder is obliged to report everything that points to a lack of efficacy as a side effect. It is, however, difficult to compare the side effects of AmBisome® one to one with Fungizone®, because Fungizone® is of a different manufacturer. Possibly, the high reporting of side effects from AmBisome® is due to the fact that AmBisome® is presently still on patent which may involves drug marketing. When Fungizone® is promoted to a lesser extent than AmBisome®, less reports will be provided to that manufacturer. A second consideration is a difference in the indications for use. There are some differences in the officially registered indications, but the question is how this is used in practice. When AmBisome® is used for other indications or more severe infections, a lack of effectiveness is more likely to be reported. Only one report actually considered an administration site condition – a report for Fungizone® - whereas most other reports communicated a lack of efficacy. With regard to the latter type of reports one has to keep in mind possible different treatment regimes in which both products are prescribed. In summary, a conclusion cannot be made on the reasons underlying the difference in reporting for this SOC.

[3] Renal and urinary disorders

The difference in renal and urinary disorders between the two types of drugs is consistent with the relevant difference found in the EMA files.

3. Comparison of side effects between Caelyx® and Doxorubicin

System/Organ Class (SOC) name	Caelyx®		Doxorubicin		summation	
	n	*%*	*n*	*%*	*n*	*%*
Blood and lymphatic system disorders	4	5.4	97	13.8	101	13.0
Cardiac disorders	2	2.7	38	5.4	40	5.2
Ear and labyrinth disorders	0	0.0	3	0.4	3	0.4
Endocrine disorders	0	0.0	1	0.1	1	0.1
Eye disorders	0	0.0	3	0.4	3	0.4
Gastrointestinal disorders	11	14.9	76	10.8	87	11.2
General disorders and administration site conditions	11	14.9	126	18.0	137	17.7
Hepatobiliary disorders	0	0.0	7	1.0	7	0.9
Immune system disorders[1]	2	2.7	4	0.6	6	0.8
Infections and infestations	7	9.5	118	16.8	125	16.1
Injury, poisoning and procedural complications	0	0.0	12	1.7	12	1.5
Investigations	0	0.0	31	4.4	31	4.0
Metabolism and nutrition disorders	0	0.0	14	2.0	14	1.8
Musculoskeletal and connective tissue disorders	1	1.4	12	1.7	13	1.7
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1	1.4	13	1.9	14	1.8
Nervous system disorders[2]	6	8.1	22	3.1	28	3.6
Pregnancy, puerperium and perinatal conditions	0	0.0	8	1.1	8	1.0
Psychiatric disorders	0	0.0	6	0.9	6	0.8
Renal and urinary disorders	1	1.4	13	1.9	14	1.8
Reproductive system and breast disorders	0	0.0	2	0.3	2	0.3
Respiratory, thoracic and mediastinal disorders[3]	9	12.2	41	5.8	50	6.5
Skin and subcutaneous tissue disorders[4]	15	20.3	11	1.6	26	3.4
Social circumstances	0	0.0	1	0.1	1	0.1
Surgical and medical procedures	0	0.0	17	2.4	17	2.2
Vascular disorders	3	4.1	24	3.4	27	3.5
Not specified	1	1.4	1	0.1	2	0.3
Total	74	100.0	701	100.0	775	100.0

[1] Immune system disorders

The difference in immune system disorders between the two types of drugs is consistent with the relevant difference found in the EMA files. Although there is a difference in percentages, the absolute numbers are very low. The specific side effects for this SOC are for Caelyx®: hypersensitivity (n=2); for Doxorubicin: hypersensitivity (n=3), and anaphylactic reaction (n=1).

[2] Nervous system disorders

The difference in nervous system disorders between the two types of drugs is consistent with the relevant difference found in the EMA files. For Caelyx® the absolute numbers are low; the different side effects within this SOC class are reported only once, except headache which is reported twice.

[3] Respiratory, thoracic and mediastinal disorders

The difference in respiratory, thoracic and mediastinal renal and urinary disorders between the two types of drugs is consistent with the relevant difference found in the EMA files. For Caelyx® the absolute numbers are low; the different side effects within this SOC class are reported only once, except distress (n=3) and interstitial lung disease (n=2). The latter, however, is recorded for Doxorubicin also 2 times and although the percentage is higher for Caelyx® the numbers are too small to conclude on a difference in side effect between the two types of drugs.

[4] Skin and subcutaneous tissue disorders

The difference in skin and subcutaneous tissue disorders between the two types of drugs is consistent with the relevant difference found in the EMA files. The difference in reporting between the two types of drugs is mainly caused by the hand-foot syndrome (palmar-plantar erythrodysesthesia). This is a side effect of several chemotherapeutic agents, but more so for liposomal chemotherapeutic agents.

4. Comparison between DaunoXome® and Cerubidine®

Although registered in the Netherlands, for DaunoXome® no reports are available at Lareb. This is probably because DaunoXome® is only approved to treat AIDS related Kaposi's sarcoma, a relatively rare condition. Because of the lack of reports on DaunoXome®, a comparison for daunorubicin between DaunoXome® and Cerubidine® with Lareb data is therefore not possible.

5. Comparison between DepoCyt® and Cytarabine

For cytarabine Lareb has a total of approximately 200 reports. Of these, however, there is only a very limited number (approximately 10) for DepoCyt®. Apart from the fact that this number is very low, the indication for DepoCyt® is also very different (Intrathecal treatment of lymphomatous meningitis) than for the other cytarabine products. This may disturb the comparison, since the underlying disease may play a role.

This document contains the Supplementary material 2 for:

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