1.1. Overview adverse events following immunization in association with Cervarix®

Introduction

Cervarix® is a vaccine for the prevention of premalignant cervical lesions and cervical cancer, causally related to Human Papillomavirus (HPV) types 16 and 18. The indication is based on the demonstration of efficacy in women aged 15 to 25 years following vaccination with Cervarix® and on the immunogenicity of the vaccine in girls and women aged ten to 25 years [1].
The vaccine has been registered in the Netherlands since September 20, 2007 and was included in the National Vaccination Program (RVP) in 2009 [1,2]. Within the RVP, three doses of the vaccine will be administered to girls at the age of twelve. In 2009 a catch up campaign for girls aged 13 to 16 years old was started [3]. Approximately 192,000 doses have been administered so far [3].
The National Institute for Public Health and Environment (RIVM) is responsible for the monitoring of adverse events following immunization (AEFI) under the RVP. An AEFI is an unwanted or unexpected event occurring after the administration of a vaccine. The event may be caused by the vaccine or may coincidently occur after immunization. Because of the differences in the assessment of adverse drug reactions following the use of medicines and adverse reactions of vaccines, this different terminology was introduced [4].
Both health professionals and consumers were able to report to the Netherlands Pharmacovigilance Centre Lareb. All reports received by Lareb were shared with the RIVM and vice versa. In this report we will give an overview of the received reports by both institutions.

Reports

On February 3, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained 575 reports concerning Cervarix®. 540 reports were initially received by the RIVM and 35 reports were directly reported to Lareb. Among the reports, 11 unique reports met the CIOMS criteria for seriousness (table 1); one case was reported to both RIVM and Lareb (85240 = 85970). Concomitant medication was not reported in these eleven cases.

Table 1. Reports on Cervarix® which met the CIOMS criteria for seriousness.

Patient, Sex, Age	Suspected adverse drug reaction	Time to onset, outcome
A 85240 = 85970 F, 11 – 20 years	headache, dizziness, afebrile convulsion, speech disorder	3 days recovered
B 86640 F, 11 – 20 years	iridocyclitis, juvenile idiopathic arthritis	1 week unknown
C 86726 F, 11 – 20 years	fever, headache, malaise, crying, meningism, nausea	1 day recovered

Patient, Sex, Age	Suspected adverse drug reaction	Time to onset, outcome
D 87105 F, 11 – 20 years	syncope vasovagal	24 hours recovered
E 88128 F, 11 – 20 years	hypotonia, syncope, pain localised, dizziness, unconscious partial, infection upper respiratory	2 days recovered
F 88877 F, 11 – 20 years	fever, hypotonia, diarrhoea, pain localised, abdominal pain, vomiting, pallor, nausea	1 day recovered
G 89464 F, 11 – 20 years	fever, syncope, pain localised, sedimentation rate increased, back pain	3 weeks unknown
H 90504 F, 11 – 20 years	syncope, dizziness, fatigue, blood pressure decreased, migraine	not reported not recovered
I 91290 F, 11 – 20 years	paralysis, unspecified, headache, muscle weakness lower limb, paraesthesia	not reported recovered
J 92677 F, 11 – 20 years	fatigue, exanthema, itching, inflammation localized, dyspnoea	not reported recovered
K 92680 F, 11 – 20 years	paralysis, unspecified, abnormal gait, paraesthesia	4 days unknown

The average number of reported AEFIs per report was 3.7, which corresponds to a total number of 2,117 reported AEFIs. The number of reported AEFI for each system organ class (SOC) is shown in table 2. The (up to) three most reported AEFI per SOC can also be found in this table.

Table 2. Number of reported AEFI associated with Cervarix® for each system organ class.

System Organ Class	Preferred Term	Number of reports	% of total
Blood and lymphatic system disorders, n=9			***0.4***
	Anaemia	1	
	Lymphadenopathy	8	
Cardiac disorders, n=4			***0.2***
	Cyanosis	3	
	Palpitations	1	
Ear and labyrinth disorders, n=5			***0.2***
	Tinnitus	2	
	Vertigo	3	
Eye disorders, n=16			***0.8***
	Lacrimation increased	4	
	Visual impairment	4	
	Mydriasis	3	
Gastrointestinal disorders, n=304			***14.4***
	Nausea	174	
	Abdominal pain	74	
	Vomiting	37	
General disorders and administration site conditions, n=802			***37.9***
	Pain	301	
	Pyrexia	182	
	Inflammation	117	
Hepatobiliary disorders, n=1			***0.0***
	Hepatic function abnormal	1	
Immune system disorders, n=2			***0.1***
	Erythema nodosum	1	
	Hypersensitivity	1	
Infections and infestations, n=11			***0.5***
	Nasopharyngitis	5	
	Upper respiratory tract infection	3	
	Pharyngitis	2	
Injury, poisoning and procedural complications, n=2		1	***0.1***
	Wound	1	
	Concussion		
Investigations, n=9			***0.4***
	Blood glucose increased	2	
	Heart rate irregular	2	
	Red blood cell sedimentation rate increased	2	
Metabolism and nutrition disorders, n=12			***0.6***
	Decreased appetite	10	
	Hyperglycaemia	2	
Musculoskeletal and connective tissue disorders, n=68			***3.2***
	Myalgia	56	
	Arthralgia	5	
	Back pain	3	

System Organ Class	Preferred Term	Number of reports	% of total
Nervous system disorders, n=485			***22.9***
	Headache	211	
	Dizziness	153	
	Syncope	20	
Psychiatric disorders, n=8			***0.4***
	Insomnia	5	
	Abnormal behaviour	1	
	Apathy	1	
Renal and urinary disorders, n=1			***0.0***
	Incontinence	1	
Reproductive system and breast disorders, n=41			***1.9***
	Menstrual disorder	36	
	Metrorrhagia	2	
	Amenorrhoea	1	
Respiratory, thoracic and mediastinal disorders, n=75			***3.5***
	Dyspnoea	26	
	Oropharyngeal pain	17	
	Cough	11	
Skin and subcutaneous tissue disorders, n=192			***9.1***
	Pruritus	59	
	Rash	59	
	Hyperhidrosis	22	
Vascular disorders, n=70			***3.3***
	Pallor	56	
	Peripheral coldness	5	
	Vasodilatation	5	
Total		***2,117***	***100.0***

Other sources of information

SmPC

The SmPC of Cervarix® mentions the following as introduction to the possible adverse reactions: *"The most common adverse reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting"* [1].

Databases

On February 3, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained 575 reports of AEFI in association with Cervarix®. On the same date the database of the World Health Organization (WHO) contained 973 AEFI reports concerning this vaccine. In comparison, the WHO database contained 2,610 reports on the other Human Papillomavirus vaccine, Gardasil®, which has been registered a year before Cervarix® and is probably more widely used than Cervarix®.

Discussion

The most reported AEFI belong to the system organ classes general disorders and administration site conditions (37.9%) and nervous system disorders (22.9%). Most of the reported events were suspected adverse reactions, like injection site reactions, pyrexia and headache.

Conclusion

This overview of AEFI associated with Cervarix® gives information about the reports about this vaccine in the Netherlands. On the basis of the current reports there is no reason to question the safety of the vaccine.

- Overview of adverse events following immunization in association with Cervarix®

References
1. Dutch SmPC Cervarix®. (version date: 20-9-2007, access date: 3-2-2010) http://eudrapharm.eu/eudrapharm/showDocument?documentId=6518768313204203285.
2. de Melker HE, Conyn-van Spaendonck M, Boot H, Coutinho R. Introductie van vaccinatie tegen baarmoederhalskanker - Stand van zaken. Ned Tijdschr Geneeskd 2009;153:A67
3. van der Maas N, Kemmeren J, de Melker H. Veiligheid van bivalent Humaan papillomavirus-vaccin. Ned Tijdschr Geneeskd 2009;153:A964
4. Bonhoeffer J, Heininger U, Kohl K, Chen RT, Duclos P, Heijbel H, Jefferson T, Loupi E. Standardized case definitions of adverse events following immunization (AEFI). Vaccine 2004;22(5-6):547-50

This signal has been raised on June 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).