

## Suspected Adverse Reaction Analysis

### CERVARIX Human papillomavirus (HPV) vaccine

04 December 2008

This report summarises the adverse reactions suspected to have been caused by Cervarix human papillomavirus (HPV) vaccine in the UK. This includes reports received between 14 April 2008 and 3rd December 2008. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)) and by the manufacturers of the vaccine as part of their legal requirements

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic<sup>1</sup> in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see <http://emc.medicines.org.uk/>).

The reactions in this report have been broken down into 5 categories based on scientific assessment of the cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)<sup>2</sup>.

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

#### Headline summary:

**To date, the vast majority of suspected adverse reactions reported to MHRA in association with Cervarix vaccine have related either to the signs and symptoms of recognised side effects listed in the product information or were due to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature).**

**For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.**

**The balance of risks and benefits of Cervarix remains positive.**

<sup>1</sup> For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.

<sup>2</sup> Using MedDRA terminology

## SUMMARY OF UK SAFETY EXPERIENCE

**Total number of reports received: 623**

**Total number of suspected reactions: 1416**

**Estimated number of doses administered to date: unavailable at present**

**Overall adverse reaction reporting rate: unavailable at present**

### A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised side-effects of Cervarix vaccine and are listed in the product information. These may occur at a frequency<sup>3</sup> of more than 1 in 10 persons vaccinated. The reported cases of 'Pain in extremity' mainly relate to a sore arm.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection-site reactions.

Reported event (Preferred Term <sup>2</sup> )	Number of cases
Pain in extremity	36
Injection site erythema	15
Limb discomfort	13
Injection site pain	10
Injection site swelling	10
Oedema peripheral	8
Erythema	5
Injection site reaction	5
Hypoaesthesia	4
Skin discolouration	4
Injection site rash	3
Local swelling	3
Pain	3
Rash macular	3
Feeling hot	2
Injection site mass	2
Injection site pruritus	2
Musculoskeletal stiffness	2
Paraesthesia	2
Injection site induration	1
Injection site inflammation	1
Injection site joint pain	1
Injection site papule	1
Injection site vesicles	1
Injection site warmth	1
Limb immobilisation	1
Local reaction	1
Pruritus	1
Total reactions	141
Total reports	106

<sup>3</sup> Based on clinical trial data

**B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)**

Allergic reactions are recognised side-effect of Cervarix vaccine and are listed in the product information. These may occur at a frequency<sup>4</sup> between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term <sup>2</sup> )	Number of cases
Rash	23
Pruritus	11
Urticaria	11
Swelling face	9
Lip swelling	7
Oedema peripheral	7
Rash pruritic	7
Eye swelling	6
Erythema	5
Dyspnoea	4
Hypersensitivity	4
Paraesthesia	4
Rash generalised	4
Anaphylactic reaction	3
Paraesthesia oral	3
Throat tightness	3
Eye pruritus	2
Ocular hyperaemia	2
Pharyngeal oedema	2
Pruritus generalised	2
Angioedema	1
Blister	1
Chest discomfort	1
Dizziness	1
Dysphagia	1
Eyelid oedema	1
Flushing	1
Gingival swelling	1
Hypoesthesia	1
Limb discomfort	1
Malaise	1
Musculoskeletal stiffness	1
Neck pain	1
Pain of skin	1
Pallor	1
Peripheral coldness	1
Purpura	1
Rash erythematous	1
Rash macular	1
Skin inflammation	1

Sneezing	1
Swelling	1
Swollen tongue	1
Type I hypersensitivity	1
Wheezing	1
Total reactions	144
Total reports	86

### C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are not side-effects of Cervarix vaccine as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

The events in the list below were considered 'psychogenic' in nature based on MHRA assessment of the individual case details reported. The reported cases which do not refer specifically to vasovagal syncope, faint or panic attack (e.g. convulsion, transient blindness which refers to temporary loss of vision at the start of a faint) were concurrently reported as signs or symptom of the psychogenic event; i.e. these also were not side-effects of the vaccine itself.

Reported event (Preferred Term <sup>2</sup> )	Number of cases
Syncope	88
Dizziness	71
Headache	43
Nausea	38
Pallor	21
Flushing	19
Malaise	16
Cold sweat	13
Tremor	13
Syncope vasovagal	9
Vomiting	9
Feeling hot	8
Paraesthesia	8
Rash	7
Vision blurred	7
Hyperhidrosis	6
Hypoaesthesia	6
Loss of consciousness	6
Somnolence	6
Unresponsive to stimuli	6
Chills	5
Abdominal pain upper	4
Dyskinesia	4
Feeling cold	4
Feeling of body temperature change	4
Visual impairment	4

Abdominal pain	3
Blindness transient	3
Convulsion	3
Dyspnoea	3
Eye rolling	3
Fatigue	3
Heart rate increased	3
Muscle twitching	3
Muscular weakness	3
Nasopharyngitis	3
Tearfulness	3
Asthenia	2
Chest discomfort	2
Confusional state	2
Dysgeusia	2
Erythema	2
Feeling abnormal	2
Hyperventilation	2
Muscle rigidity	2
Myalgia	2
Nervousness	2
Peripheral coldness	2
Pulse abnormal	2
Rash macular	2
Stomach discomfort	2
Tinnitus	2
Abasia	1
Altered state of consciousness	1
Anxiety	1
Blindness	1
Body temperature increased	1
Bruxism	1
Burning sensation	1
Chest pain	1
Colour blindness	1
Cyanosis	1
Deafness	1
Deafness transitory	1
Discomfort	1
Disorientation	1
Dizziness postural	1
Dry mouth	1
Dry throat	1
Dysphagia	1
Dysstasia	1
Ear pain	1
Eye swelling	1
Eyelid oedema	1
Facial spasm	1
Fall	1
Feeling of despair	1
Grand mal convulsion	1
Heart rate irregular	1

Hot flush	1
Hypersomnia	1
Lethargy	1
Lip swelling	1
Musculoskeletal stiffness	1
Mydriasis	1
Neck pain	1
Oropharyngeal pain	1
Pain	1
Panic reaction	1
Photophobia	1
Pruritus	1
Pyrexia	1
Rash generalised	1
Respiratory arrest	1
Respiratory rate decreased	1
Respiratory rate increased	1
Salivary hypersecretion	1
Seizure anoxic	1
Sensory loss	1
Shock	1
Swelling face	1
Tachycardia	1
Throat irritation	1
Throat tightness	1
Total reactions	540
Total reports	205

#### D. 'Other recognised' reactions

This section includes other events recognised to be side-effects of Cervarix vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term <sup>2</sup> )	Number of cases
Headache	102
Nausea	90
Dizziness	88
Vomiting	35
Abdominal pain upper	18
Fatigue	18
Malaise	18
Pyrexia	12
Abdominal pain	10
Myalgia	7
Chills	5
Feeling hot	5

Stomach discomfort	5
Arthralgia	4
Diarrhoea	4
Paraesthesia	4
Body temperature increased	3
Oropharyngeal pain	3
Pain	3
Pain in extremity	3
Back pain	2
Feeling of body temperature change	2
Influenza like illness	2
Musculoskeletal stiffness	2
Neck pain	2
Pallor	2
Pruritus	2
Thirst	2
Asthenia	1
Induration	1
Lethargy	1
Listless	1
Local swelling	1
Lower respiratory tract infection	1
Migraine	1
Musculoskeletal chest pain	1
Nasal congestion	1
Pharyngitis	1
Pruritus generalised	1
Rash	1
Respiratory disorder	1
Skin warm	1
Somnolence	1
Tremor	1
Upper respiratory tract infection	1
Urticaria	1
Wheezing	1
Total reactions	472
Total reports	252

### E. Suspected adverse reactions not currently recognised

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of Cervarix vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

System Organ Class	Reported event (Preferred Term <sup>2</sup> )	Number of cases	
Blood and lymphatic system disorders	Lymphadenopathy	4	
Cardiac disorders	Palpitations	1	
Ear and labyrinth disorders	Ear pain	3	
Eye disorders	Eye swelling	1	
	Photophobia	1	
	Vision blurred	3	
Gastrointestinal disorders	Abnormal faeces	1	
	Mouth ulceration	1	
	Nausea	2	
	Vomiting	3	
General disorders and administration site conditions	Abasia	1	
	Chills	1	
	Fatigue	1	
	Feeling cold	1	
	Influenza like illness	5	
	Local swelling	1	
	Malaise	3	
	Oedema peripheral	2	
	Pain	1	
	Peripheral coldness	2	
	Swelling	1	
	Infections and infestations	Application site pustules	1
		Folliculitis	1
Nasopharyngitis		1	
Pneumonia viral		1	
Injury, poisoning and procedural complications	Contusion	3	
	Drug exposure during pregnancy	1	
Investigations	Blood glucose increased	2	
	Blood pressure increased	1	
	Respiratory rate increased	1	
	Weight decreased	1	
Metabolism and nutrition disorders	Anorexia	1	
	Dehydration	1	
	Diabetes mellitus inadequate control	1	



	Diabetic ketoacidosis	1
	Hypoglycaemia	1
Musculoskeletal and connective tissue disorders	Muscular weakness	2
	Musculoskeletal stiffness	1
	Myalgia	1
	Pain in extremity	5
Nervous system disorders	Complex regional pain syndrome	1
	Convulsion	2
	Dizziness	2
	Facial palsy	1
	Grand mal convulsion	1
	Hemiparesis	1
	Hypoaesthesia	2
	Lethargy	1
	Migraine	1
	Paraesthesia	2
	Somnolence	5
	Status epilepticus	1
	Syncope	2
	Tremor	1
	Unresponsive to stimuli	1
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1
Psychiatric disorders	Confusional state	1
	Insomnia	1
	Sleep disorder	2
Reproductive system and breast disorders	Amenorrhoea	1
Respiratory, thoracic and mediastinal disorders	Asthma	1
	Dyspnoea	2
	Epistaxis	2
	Haemoptysis	1
	Hypoventilation	1
	Nasal congestion	1
	Oropharyngeal pain	3
	Wheezing	1
Skin and subcutaneous tissue disorders	Eczema	2
	Erythema	1
	Guttate psoriasis	1
	Rash	2
	Rash vesicular	1
	Skin discolouration	2
Vascular disorders	Flushing	1
	Pallor	1
Total reactions		119
Total reports		71

In relation to safety in pregnancy, during pre-licensing studies of Cervarix it was found that almost 870 women became pregnant before or after receiving the vaccine. The overall rates of spontaneous abortion in these clinical trials were no greater than the background rates in the general population (i.e. regardless of vaccination). There is currently no evidence to suggest that Cervarix vaccine carries any risks during pregnancy. Nonetheless, Cervarix is not recommended for use in pregnancy.