Gardasil – Update on National Monitoring Experience

11th November 2010

The HSE human papillomavirus (HPV) School Immunisation Programme commenced in May 2010 and it is estimated that 60,000 doses of Gardasil have been distributed and approximately 45,000 doses have been administered up to the end of October 2010.

The Irish Medicines Board has received a total of 64 reports of adverse events associated with use of Gardasil up to the end of October 2010, 55 of which were received since the beginning of the schools immunisation programme. Suspected adverse reaction reporting rates are highly variable and are dependent on many factors. Therefore these data cannot be used to determine the frequency of occurrence of adverse reactions to Gardasil. A single report may include more than one suspected reaction.

The majority of the reports have been consistent with the expected pattern of adverse effects for the vaccine, as outlined in the product information, and include cases of injection site reactions, malaise, headache, dizziness, fainting, fatigue and gastrointestinal symptoms. There have been two reports of seizures, one occurring in a patient with a history of epilepsy.

Vaccination related events most commonly reported include reports of syncope (faints), sometimes in conjunction with seizure-like movements, along with reports of dizziness and hyperventilation. Healthcare professionals are reminded that patients should be carefully observed for an appropriate period of time after administration of Gardasil (see Summary of Product Characteristics for further information). In accordance with local guidance patients should be in a seated position during vaccination administration and should remain in the vicinity of the place of vaccination for up to 15 minutes.

Reports of allergic reactions have also been received including two patients who experienced anaphylactic-type reactions, both of whom recovered without sequelae. Among the allergic reactions, reported symptoms included rash, urticaria and flushing.

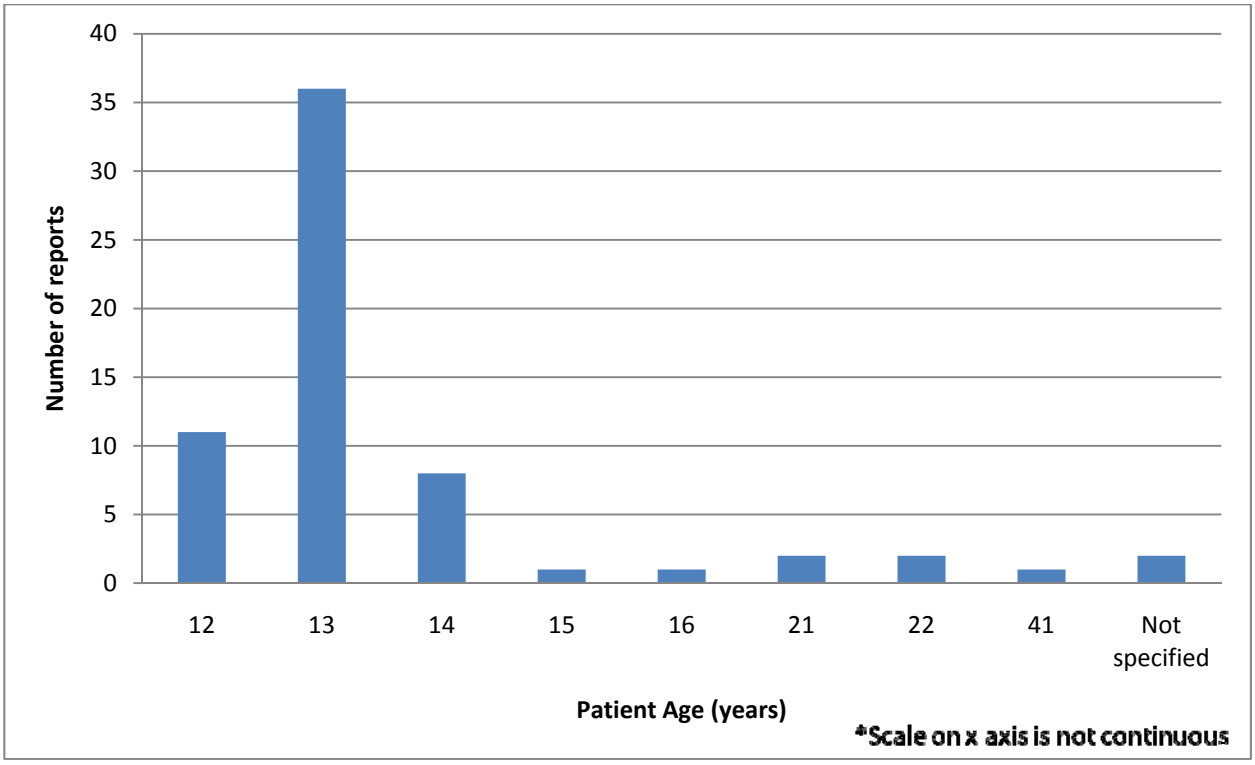
Anaphylaxis is a very rare side effect of most vaccines. Appropriate medical treatment and supervision should always be readily available in case of a serious allergic reaction and possibly a rare anaphylactic event following the administration of the vaccine.

Gardasil should not be used in people who may be hypersensitive (allergic) to the active substance or any of the other ingredients. Patients who show signs of an allergy after a dose of Gardasil should not receive further doses of the vaccine. Vaccination should be postponed in patients who are ill with a high fever.

The IMB together with the European Medicines Agency will continue to closely monitor the benefit-risk profile of Gardasil. The balance of risks and benefits for the vaccine remains positive. Healthcare professionals and members of the public are encouraged to report all suspected adverse reactions using the online Adverse Reaction Report form. A downloadable version of the Adverse Reaction Report form is also available, which can be filled in manually and sent to the IMB by freepost.

Breakdown of Reports by Patient Age:

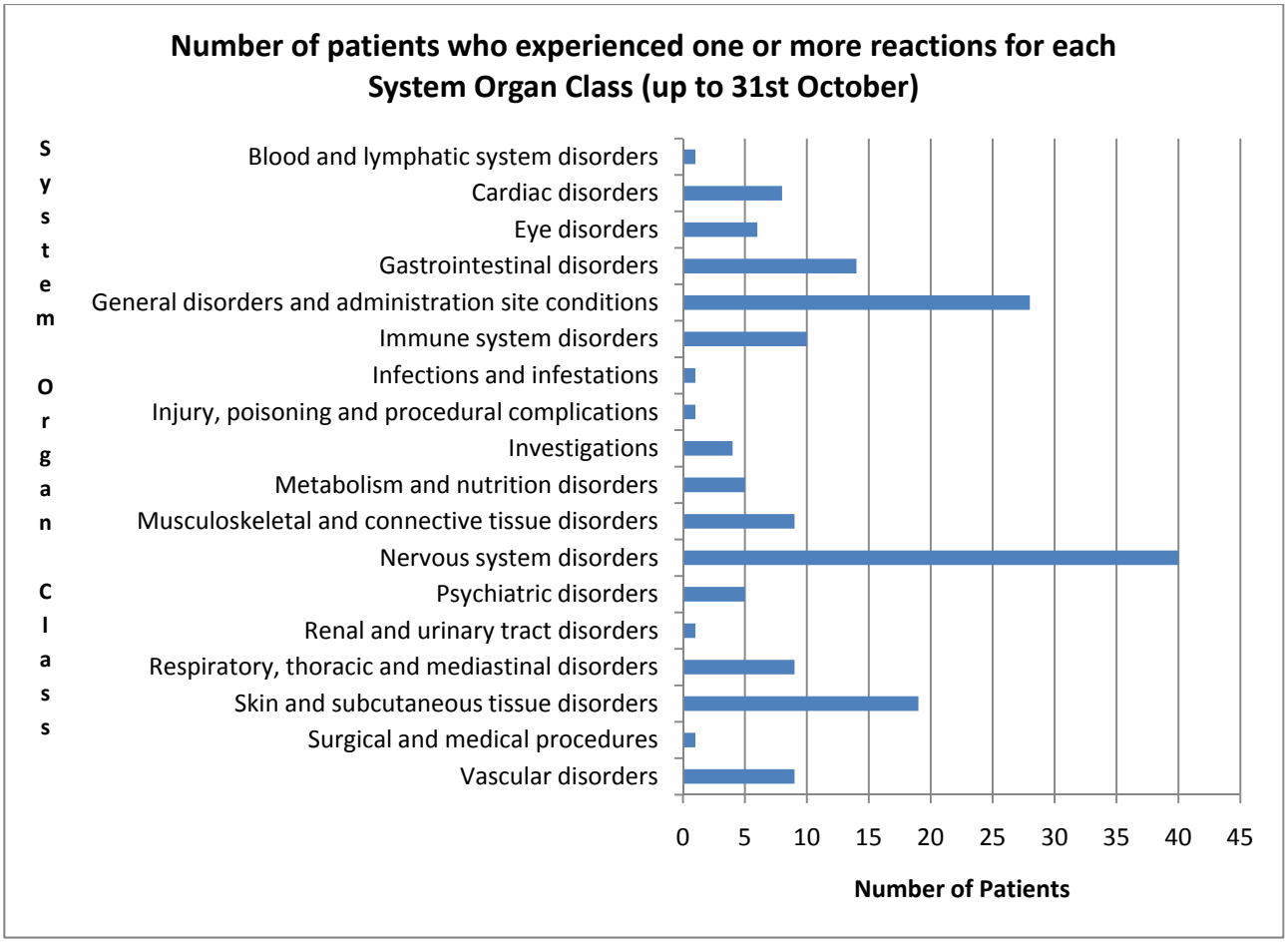
Up to October 31st 2010 the majority of reports received have been in the 12-14 years age group which is as expected given the target population for the HPV vaccines School Immunisation Programme. As illustrated below, some reports have been associated with use in older women vaccinated outside the context of the School Immunisation Programme.



Distribution of Adverse Reactions by System Organ Class (SOC):

Symptoms described on adverse drug reaction reports are coded to an internationally recognised standard terminology known as MedDRA (Medical Dictionary for Regulatory Activities). MedDRA is a medical terminology used to classify adverse event information associated with the use of medical products so that similar events can be counted together. Each event is given an appropriate description (the 'preferred term') and is grouped according to the body system or organ it affected (the 'system organ class' or 'SOC'). Use of such terminology supports data review and analysis and facilitates common understanding and exchange of information across organisations.

As outlined above a single patient may experience several reactions that will be included in a single report thus the number of reactions may not be equal to the number of patients.



The most frequently reported suspect adverse reactions in each system organ class (SOC) experienced by patients since first authorisation of Gardasil are listed below:

- Nervous System disorders: dizziness, syncope, headache *
- General disorders and administration site conditions: fatigue, asthenia, malaise
- Skin and subcutaneous tissue disorders: rash, erythema, pruritis
- Gastrointestinal disorders: nausea, vomiting, abdominal discomfort
- Immune system disorders: anaphylactic reaction, hypersensitivity, urticaria
- Respiratory, thoracic and mediastinal disorders: hyperventilation, cough, dyspnoea
- Vascular disorders: pallor, hypotension, flushing
- Cardiac disorders: cyanosis, tachycardia, chest discomfort
- Musculoskeletal and connective tissue disorders: pain in extremity, myalgia, back pain
- Eye disorders: photophobia, eyelid oedema, eyelid pruritus
- Metabolism and nutrition disorders: tetany**,** polydipsia, appetite decreased
- Psychiatric disorders: anxiety, panic attack, emotional distress
- Investigations: blood glucose increased, heart rate irregular, weight decreased
- Infections and infestations: viral infection
- Injury, poisoning and procedural complications: contusion
- Blood and lymphatic system disorders: lymphadenopathy
- Surgical and medical procedures: off label use
- Renal and urinary tract disorders: ketonuria

* Psychogenic events (which appear mainly as Nervous System Disorders) include vasovagal events, syncope (faints), panic attacks and associated symptoms. These can occur with any injection procedure, not only vaccination, and can be common in adolescents. Such events may be associated with a wide range of temporary signs and symptoms including: loss of consciousness; vision disturbance; injury; limb jerking (which may be misinterpreted as a seizure or convulsion); limb numbness or tingling; and difficulty in breathing or hyperventilation. These may be due to fear or anticipation of the injection and are not side effects of the vaccine as such.

Understanding the Data Reported to the IMB

These adverse reaction reports have been submitted to the IMB on a voluntary basis by healthcare professionals and members of the public, either through the online reporting tool available on the IMB website (www.imb.ie), or by post or telephone. This report also contains any Irish reports notified to the IMB by the Marketing Authorisation holder for Gardasil (Sanofi Pasteur MSD) in accordance with legislation.

Reporters are encouraged to report *suspected* adverse reactions. In other words, the reporter does not have to be sure that the vaccine caused the reaction, a mere suspicion will suffice. Therefore the reports received may be true adverse reactions to the vaccine, they may be events related to the process of vaccination rather than to the specific vaccine itself, or they may be coincidental events which have occurred post-vaccination but which would have occurred anyway even if vaccination had not taken place (e.g. they may be due to an underlying medical condition).

More information on Gardasil, including information on recognised adverse effects, can be found in the product information (Summary of Product Characteristics and Package Leaflet, available on the Irish Medicines Board website at www.imb.ie or the European Medicines Agency website www.ema.europa.eu) or by contacting your doctor.