IRISH MEDICINES BOARD

UPDATE ON NATIONAL MONITORING EXPERIENCE WITH PANDEMIC H1N1 VACCINES

Suspected Adverse Reactions to Pandemic (H1N1) 2009 Vaccines occurring in Ireland

17th December 2009

The H1N1 vaccines in use in Ireland are Pandemrix and Celvapan. It is estimated that approximately 1.5 million doses have been distributed and that some 500,000 doses have been administered in Ireland to date.

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 the H1N1 vaccines. Additionally, the use of the two H1N1 vaccines available in Ireland may differ in terms of the extent of use and the patient populations exposed. For these reasons, the data provided in this update should not be used to draw comparisons on the safety of the vaccines. Guidance on interpreting the data presented is provided at the end of this report.

Up to Wednesday 16th December 2009, 790 reports of suspected adverse reactions to the Pandemic H1N1 vaccines (Pandemrix and Celvapan) have been received by the Irish Medicines Board (IMB). A single report may include more than one suspected reaction.

The reports received to date remain consistent with the expected pattern of adverse effects for the pandemic vaccines. The balance of risks and benefits for Celvapan and Pandemrix remains positive.

Pandemrix

The IMB has received 435 adverse reaction reports for Pandemrix. The most frequently reported suspected adverse reactions were injection site reactions (e.g. pain, swelling, redness), gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and flu-like symptoms (e.g. pain, fever, fatigue and swollen glands).

Among the commonly reported reactions were other vaccination-related events which were generally non-serious and resolved without treatment.These included dizziness, syncope (fainting episodes), headache, paraesthesia (pins and needles) and transient limb weakness in the vaccinated limb. The IMB has received one report of neuralgia like pain which resolved two days post-vaccination.

The IMB has received 30 reports of allergic reactions to Pandemrix. Reported symptoms included rash, flushing and dyspnoea and less frequently urticaria, facial oedema (periorbital swelling/swelling of lips/tongue), hypotension, tachycardia and wheezing. Some of the allergic reactions occurred in patients without a history of anaphylactic reactions or known drug/food allergies. Allergic reactions are a recognised potential adverse reaction. The reports of allergic reactions indicate that not only allergy to substances in the vaccine such as egg may give rise to reactions, but also other forms of allergic tendency appear to contribute to the development of an allergic reaction.

There have been three reports of facial palsy occurring post-vaccination including two reports of Bell's Palsy. A causal relationship with vaccination has not been established. A case of facial weakness has also been reported and the patient recovered without sequelae.

There have been three reports of seizures, one of which occurred in a patient receiving treatment for epilepsy. The second case was a febrile convulsion in a child with a history of previous febrile convulsions. Another case involved a patient with no prior history of epilepsy who had a recent pre-vaccination diagnosis of a neurological condition. Investigation of this case is ongoing.

One report of suspected Guillain Barré Syndrome (GBS) has been reported and further information is awaited to facilitate assessment of this case.. Experience to date does not suggest that the vaccine contributes to the occurrence of Guillain-Barré syndrome.

The IMB has received 12 adverse reaction reports associated with the use of Pandemrix in pregnant women*. The reactions reported involved expected effects, including local injection-site reactions, gastrointestinal symptoms, flu-like symptoms (e.g. fever) and vaccination-related events such as syncope and dizziness.

The IMB has been notified of a case of spontaneous abortion (miscarriage) in a woman with a history of recurrent miscarriage. There is currently no evidence to suggest that the vaccine contributed to this event.

One hundred and fifty-seven adverse reaction reports were associated with use in children and these included injection site reactions, flu-like symptoms, gastrointestinal symptoms as well as vaccination related events (including pallor and syncope). To date, the IMB has received 11 reports of allergic reactions in children, a number of which were serious requiring treatment/hospitalisation. There have been 27 reports of pyrexia (fever) in children, fifteen of which occurred in children aged 3-10 years and 5 in those aged 6-35 months.

Celvapan

The IMB has received 337 adverse reaction reports for Celvapan. These include injection site reactions, flu-like illness and allergic-type reactions. Among the commonly reported adverse reactions were nervous system disorders such as headache, dizziness, paraesthesia and syncope. There have also been reports of gastrointestinal symptoms, particularly nausea and vomiting, some of which were serious and required treatment.

There have been 33 reports of allergic reactions to Celvapan, including three reports of suspected anaphylaxis. Among the allergic reactions, the reported symptomology most commonly included rash, urticaria and pruritis and in a smaller number of cases hypotension, tachycardia and respiratory effects. Serious allergic reactions have been reported in patients without a known history of allergy as well as in patients with a history of allergies or chronic conditions such as asthma and eczema. The IMB has received three reports of suspected anaphylactic reaction to Celvapan. In all cases, symptoms resolved following treatment.

The IMB has been made aware of the death of a patient 10 days post vaccination with Celvapan. The patient had a number of underlying conditions including complex cardiac disorders and insulin-dependent diabetes. There is no evidence of a causal relationship between vaccination and the patient's death.

There have been four reports of seizures, two of which occurred in adults receiving treatment for epilepsy. One case described a seizure in a patient who experienced pallor and felt faint after vaccination but recovered fully without treatment. The most recent case

was reported as an afebrile seizure in a child occurring two days post-vaccination and follow up information is awaited.

The IMB has received one report of a suspected exacerbation of an autoimmune disorder – symptoms resolved with treatment.

Thirty reports were associated with use in pregnant women and included gastrointestinal symptoms, flu-like symptoms (including fever), syncope and other vaccination related events (e. g. anxiety, palpitations, dizziness). There have been four reports of allergic-type reactions.

The IMB has been notified of a case of spontaneous abortion (miscarriage) in a woman with a history of recurrent miscarriages. There is currently no evidence to suggest that the vaccine contributed to this event.

One hundred and forty reports were associated with the use of Celvapan in children and these primarily included non-serious expected reactions such as injection site reactions, gastrointestinal symptoms, flu-like symptoms, skin rashes and vaccination related events (e.g. feeling faint, pallor and syncope). The IMB has received 18 reports of allergic-type reactions in children, some of which have been serious and required treatment. There have also been four reports of transient hypotonia in some cases with other symptoms (i.e. post-vaccination events e.g. syncope and/or allergic type reactions). Nine reports of pyrexia (fever) in children have been received, all occurring in children less than 10 years of age.

Brand unknown
The vaccine brand was not reported in 18 cases and follow up to establish which product was used is underway. These include reports of flu-like symptoms, injection site reactions, vaccination-related events (e.g. dizziness and two reports of seizures).

Vaccine Traceability

- Healthcare professionals and members of the public are requested wherever possible to include details of the brand name/manufacturer of the vaccine administered when submitting adverse reaction reports.

- It is very important that the name of the vaccine administered is recorded in healthcare/patient records and that patients are provided with a copy of the package leaflet supplied with the vaccine to ensure that they are aware of the brand of vaccine administered.

Advice to Healthcare Professionals and Caregivers

- The IMB wishes to remind healthcare professionals that, as with all injectable 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. An appropriate post-vaccination monitoring period should be observed in line with local guidance and recommendations on vaccination.

- Monitoring of temperature is recommended in young children following vaccination. As with all vaccines, prescribers and parents should monitor the temperature of the vaccinated child and, if necessary, take measures to lower the fever (e.g. giving an antipyretic such as paracetamol).

- The IMB wishes to remind healthcare professionals that there are no safety, immunogenicity or efficacy data to support interchangeability of Pandemrix and Celvapan.

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 holders for Pandemrix (GSK) and for Celvapan (Baxter).

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).

All reports are carefully evaluated and one objective of this evaluation is to distinguish real side effects from coincidental medical events. Many people receiving the vaccine have serious and/or chronic underlying medical conditions which put them at greater risk of developing serious complications of swine flu. This is why it is important for these people to be vaccinated as a priority. Over the next few months, many of these patients may naturally suffer an exacerbation of their underlying illness and as a result some may subsequently die from their illness. Such events may coincidentally occur around the time of vaccination and as such, may be reported to the IMB. It is important to bear in mind that this temporal association does not in itself mean that the vaccine was responsible for the event and that the timing may be purely coincidental.

Complications can occur in any pregnancy and information from the Royal College of Obstetricians indicates that in Ireland up to 20% of pregnant women miscarry during the first 14 weeks of pregnancy, and still-births occur in 8-10 pregnancies per 1,000. Therefore, it is inevitable that some adverse pregnancy outcomes will occur with pregnant women, some of whom will have been vaccinated.

Guillan-Barré Syndrome is a naturally occurring condition so it is inevitable that cases will occur, and be reported as possible side effects, not long after vaccination, particularly over the winter period when many pathogens are circulating. It is important to understand that a temporal association alone does not mean that the vaccine caused the condition. There are excellent systems in place to detect if the vaccine may be causing conditions such as GBS and the IMB isworking very closely with its European and international partners in monitoring vaccine safety. It is estimated that at least 26 million doses of H1N1 vaccine have now been administered across Europe and there is no evidence to suggest that the vaccines are causing GBS.

More information on Pandemrix and Celvapan, including information on recognised adverse effects, is provided in the production information, copies of which are available from the IMB and European Medicines Agency websites (http://www.inb.ie and http;//emea.europa.eu).

**Number of pregnancy cases revised from previous update to reflect follow-up information since received which clarified initial reports.*