IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

SPECIAL EDITION

IMB Update on Pandemic A(H1N1)v vaccines

Pandemrix Vial Label

Early batches of the GSK vaccine, Pandemrix, were manufactured prior to approval of the final label. These batches have a slightly different vial label to the later batches but are of an equivalent quality and are appropriate for use. The difference is that the vial label does not include the trade name 'Pandemrix' but instead is labeled as PrePandemic/Pandemic Influenza Vaccine. The outer packaging and product literature includes the name 'Pandemrix'.

Any reports of suspected adverse reactions should include the trade name, Pandemrix, and the batch number. It is recommended that patient records should include the trade name, Pandemrix, and the batch number of the vaccine administered to ensure traceability. Stickers will be supplied with the vaccines, which include the trade name 'Pandemrix' and the batch number to facilitate traceability.

The European Commission on the recommendation of the European Medicines Agency (EMEA) has granted licences for three vaccines against influenza A(H1N1)v. These vaccines are:

Celvapan (Baxter),
Pandemrix (GlaxoSmithKline).
Focetria (Novartis),

The IMB understands that the Baxter vaccine, **Celvapan** and the GSK vaccine, **Pandemrix**, will be made available in Ireland by the Department of Health and Children in accordance with the national immunisation strategy for the pandemic. Consequently, both products are the focus of this update. These 'pandemic' vaccines were licensed using the so-called 'mock-up' approach. This approach involved the development of 'mock-up' vaccines in advance of the pandemic, based on information generated with a different virus strain that could have itself caused a pandemic (an H5N1 influenza virus strain). Once the A(H1N1)v virus strain causing the current pandemic was identified by the World Health Organisation (WHO), the manufacturers were able to replace the H5N1 strain in the 'mock-up' vaccines with the H1N1 strain resulting in the final 'pandemic' vaccines for use now.

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The 'pandemic' vaccines were licensed on the basis of information on quality, safety and immunogenicity, including information from clinical trials involving more than 6,000 subjects, generated at the time of the licensing of the mock-up vaccines, as well as on information relating to the change in strain from H5N1 to H1N1. Further clinical trials in adults and in children are ongoing and more results will become available in the coming weeks and months.

Product Information

Details of the Product Information for each of the vaccines including the Summary of Product Characteristics (SmPC) and the Package leaflet (PL) are available on the IMB and EMEA websites, as is an EU explanatory document on the scientific considerations regarding the licensing of the pandemic vaccines. It is strongly recommended that the Product Information is read in conjunction with this explanatory document as it provides further detailed information on the use of these vaccines.

Extensive amounts of new safety and efficacy data are expected from the widespread use of the vaccines in vaccination programmes across the EU. Procedures are in place to allow for the rapid review of all such data and it is likely that the product information (SmPC and PL) will be updated at regular intervals. Healthcare Professionals are requested to monitor the IMB and EMEA websites throughout the pandemic for updated information as it becomes available.

Current Recommendations on Dosage

The current recommendation is for a two-dose vaccination schedule, at an interval of three weeks, for adults, including pregnant women, and children from six months of age. The IMB anticipates the availability of further data from ongoing clinical studies over the coming months and these recommendations may be updated.

Use of the vaccines in Pregnancy

The available evidence suggests that in pregnant women the risk for complications due to seasonal influenza increases with the duration of pregnancy with the risk being lower in the first trimester, but not negligible. The risk was highest during the third trimester. Moreover, the presence of co-morbidities in a pregnant woman strongly increased the risk of complications.

Clinical trials with the 'mock-up vaccines' and to some extent the vaccines that include the A(H1N1)v strain provide immunogenicity results in women of childbearing age. Based on experience from other influenza vaccines, it is assumed that immunogenic responses in non-pregnant women can be extrapolated to pregnant women.

The current recommendation is a two-dose vaccination schedule for pregnant women, at an interval of three weeks. Vaccine safety in pregnant women and effectiveness will be closely monitored, as part of the post-marketing surveillance plan. Observational studies using established pregnancy registries are planned.

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Use of the vaccines in Children

With respect to pandemic influenza vaccines, limited data have been collected in children within the development of 'mock-up' vaccines. The current recommendation is for a two-dose vaccination schedule, at an interval of three weeks, for children from six months of age. Paediatric studies with A(H1N1)v are currently ongoing with all pandemic vaccines, and the IMB is expecting further data from these studies over the coming months and the recommendation may be updated.

Known Safety profile

Most of the adverse events seen to date in relation to these vaccines were in clinical trials with the H5N1 strain and were mild in nature, of short duration and qualitatively similar to those induced by seasonal influenza vaccines. There were fewer reactions after the second dose of the vaccine compared with the first dose. The most frequently occurring adverse reaction was injection site pain, which was usually mild. Other common side effects reported in trials to date were fatigue, malaise, induration, erythema, swelling, pruritis and bleeding at the injection site. Pyrexia, sweating, chills, headache, lymphadenopathy, arthralgia and myalgia were also commonly reported.

Thiomersal

Pandemrix contains thiomersal, a compound containing mercury that is used as a preservative in medicines. The use of thiomersal in Pandemrix extends the time-period over which the multi-dose vial of the vaccine may be used.

Based on a large amount of scientific data, the WHO and the EMEA have concluded that the evidence favours the rejection of a causal relationship between thiomersal-containing vaccines and autism. Additional publications have underscored the lack of an association between thiomersal and neuro-developmental disorders.

A European Review previously concluded that there is no evidence of harm from thiomersal in vaccines other than the possibility of hypersensitivity (allergic) reactions. The presence of thiomersal in the composition of vaccines is stated on the label and a warning regarding the risk of sensitisation in relation to thiomersal and other preservatives is included in the product information. The IMB wishes to emphasise that immunisation with vaccines containing thiomersal continues to offer valuable benefits to the general population, including infants. The benefits of vaccination far outweigh the risks, if any, of exposure to thiomersal-containing vaccines.

Adjuvant

Pandemrix contains an 'adjuvant' (a substance that enhances the immune response so that less viral material can be used in each dose of vaccine). Benefits of using an adjuvant include better cross-protection against drifted influenza strains, as suggested by results with H5N1 vaccines, and increased production capacity potentially improving vaccine availability. The adjuvant in Pandemrix (ASO3) has been tested in clinical trials involving several thousand subjects and the safety profile is considered to be acceptable.

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Post Marketing safety of the Vaccines

Advice to Healthcare Professionals on Pandemic Pharmacovigilance

As limited safety data on novel H1N1 influenza vaccines are currently available, additional pharmacovigilance activities are essential to monitor and assess their safety with widespread use.

It is critical that healthcare professionals report all serious suspected adverse reactions to the IMB as soon as possible and with sufficient detail to support evaluation.

As new safety data become available, the IMB will work with its EU counterparts to establish appropriate risk minimisation measures to support the continued safe and effective use of these medicines. The prompt identification of a safety concern during a pandemic will rely on the detection and reporting of adverse reactions to the IMB. Due to the possible disruption of the postal system and limited time available to healthcare professionals, the IMB recommends that healthcare professionals should, where feasible report adverse reactions using the on-line reporting system.

The IMB has developed a special web-based system for reporting suspected adverse drug reactions associated with pandemic vaccines. This on-line reporting system is accessible via the pandemic flu webpage on the IMB homepage (**www.imb.ie**). This is available now and will continue to operate for the duration of the pandemic. An illustrative copy of the pandemic adverse reaction on-line reporting form is included with this Bulletin along with advice on what information should be included in a report (see attached insert).

The IMB requests that healthcare professionals provide details of:

- Vaccine trade name (it is essential to specify the trade name of the vaccine to facilitate differentiation from the seasonal influenza vaccine)
- Batch number
- Dates of initial and second (if applicable) vaccination
- Date of onset of the reaction
- Treatment received
- Outcome of the reaction
- Relevant medical history
- Age and gender of the patient

For clusters of reactions, please provide details of the vaccination setting and any relevant information on in-use conditions.

In relation to the pandemic vaccines, the IMB requests that health care professionals particularly report the following suspected adverse reactions/post-immunisation events:

- Serious unexpected adverse reactions
- Adverse events of special interest (AESI):
  - neuritis,
  - convulsions,
  - anaphylaxis,
  - encephalitis,
  - vasculitis,
  - Guillain-Barré syndrome,
  - Bell's palsy,
  - demyelinating disorders,
  - vaccination failure.

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