European Medicines Agency

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Addendum 1
on
pandemic influenza A(H1N1)v vaccines authorised via the core dossier procedure[1]

Explanatory note on scientific considerations regarding the dosage and co-administration with seasonal vaccines recommendations update for pandemic A(H1N1)v vaccines

Further to the strain changes of the mock-up vaccines from H5N1 to H1N1v which were approved in September 2009 (please refer to the Explanatory note on scientific considerations regarding the licensing of pandemic A(H1N1)v vaccines) the Committee for Medicinal Products for Human Use (CHMP) has been carefully looking at H1N1 data as it is available for assessment.

This explanatory note provides an update of the scientific rational the CHMP has used in order to reach its conclusion on the recent update regarding dosage and co-administration with seasonal vaccines recommendations for pandemic influenza vaccines.

Dosage (posology)

The data obtained with the mock-up vaccines in various age groups indicated the need for a two-dose priming schedule (i.e. administration of two doses at least three weeks apart) in order to achieve immune responses that met the criteria laid down in CHMP guidance documents for candidate pandemic vaccines. In the studies with mock-up vaccines the majority of subjects had no detectable antibody (based on a commonly used test that examines inhibition of haemagglutination) to the H5N1 strains used before the first dose was given (i.e. were seronegative at baseline). Therefore it was considered that mock-up vaccines that elicited immune responses meeting the CHMP criteria against H5N1 would be suitable to predict immune responses to the same vaccine formulations containing a pandemic strain to which the majority of the population has no pre-existing immunity.

However, the limited data available from ongoing clinical studies with the pandemic H1N1v vaccines have shown that variable but sometimes substantial proportions of subjects in some age sub-groups are already seropositive with respect to the vaccine strain at baseline.
In order to fully assess the potential for these vaccines to protect against clinical disease the CHMP has paid special attention to the immune responses in subjects who are seronegative with respect to the pandemic strain before vaccination. In contrast to the results obtained with the mock-up vaccines, the immune responses in healthy individuals in certain age sub-cohorts to a first dose of some of these pandemic vaccines have met the criteria laid down in CHMP guidance whether or not subjects were seropositive or seronegative at baseline. At present there are no data in subjects with co-morbid condition generally qualifying for vaccination programs. There are no data on long-term persistence of antibodies following a single dose vaccination.

[1] Addendum to document EMEA/608259/2009, published at:
http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/60825909en.pdf

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There are very few data available as yet regarding pre-vaccination seropositivity rates and immune responses to the three pandemic vaccines currently licensed in the centralised procedure (including administration of adult and half-adult doses) in children and adolescents. The minimum criteria for immune responses laid down in CHMP guidance are not derived from experience in children and it is not known if the criteria are wholly applicable, especially in the youngest children (e.g. those aged less than 3 years) who are the most likely to lack any degree of pre-existing immunity to influenza viruses. Due to these concerns the CHMP is currently requesting provision of data on immune responses in children using more than one method of assessment and after first and second doses to provide a more robust assessment of the antigen dose and the number of doses required.

Based on the results currently available from ongoing individual pandemic vaccine studies in healthy subjects the CHMP has indicated for Pandemrix and Focetria that a single dose may be sufficient in specific age ranges. Further data are necessary however to confirm that one dose is indeed sufficient. Therefore the CHMP has not made a definitive recommendation for a single dose. Especially certain patient groups (e.g. the immunocompromised) may benefit from a second dose. Data in these groups will be generated during the course of the pandemic.

However, the CHMP recognises that it may not be possible during the current pandemic to determine whether a second dose offers an additional benefit. It is possible that increments in antibody levels will be seen after second doses of these vaccines but such observations may not suggest a benefit for two doses in terms of protection against clinically apparent infection when the responses to the first dose are already very high.

Longer-term data on persistence of antibody or a demonstration of better cross-reactivity of antibody to drifted variants after two doses versus one dose will be of interest. However, even these data may not provide a definitive answer regarding any potential benefit of a second dose since the priming afforded by the first dose may be the more critical factor. A definitive answer regarding the degree and duration of protection afforded by a single dose will likely come only from documentation of breakthrough cases in subjects who received single doses versus those subjects who received 2 doses and those subjects who were not vaccinated, including cases due to drifted strains. The accumulation of such data may take some considerable time and therefore the current dose recommendations have to rely on the available data on immune responses measured at approximately three weeks after each of the first and second doses. Given these uncertainties currently CHMP can not endorse dose recommendations to one dose for all target populations for vaccination.

The CHMP acknowledges that dosing recommendations in Europe may differ from those given by other regulatory agencies worldwide. The differences observed have stemmed from differences in the way the vaccines are produced and in the approaches taken for their authorisation.
It is also possible that changes in the characteristics of the pandemic itself could prompt the CHMP to modify the dose recommendations. The CHMP recommendations will be updated as more data become available.

Co-administration with seasonal influenza vaccines

Data on co-administration of non-adjuvanted seasonal influenza vaccine with Pandemrix H1N1 in healthy adults aged over 60 years, and with Focetria (H1N1) in healthy adults aged 18-60 years have been submitted. The data do not suggest any significant interference of non-adjuvanted seasonal influenza vaccines with the immune response to Pandemrix H1N1 or Focetria H1N1. The immune response to seasonal antigens was also satisfactory.
Co-administration was not associated with higher rates of local or systemic reactions compared to administration of the pandemic vaccine alone.
Therefore the available data indicate that Pandemrix and Focetria may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into opposite limbs).

For Celvapan, there are currently no data on co-administration with other vaccines, therefore the recommendations previously agreed remain. However, if co-administration with another vaccine is considered, immunisation should be also carried out on separate limbs. It should be noted that the adverse reactions may be intensified. Data on co-administration with a seasonal influenza vaccine are expected shortly.

For further information on the assessment of the available data please refer to the scientific discussions published in the European Public Assessment Report (EPAR) for Celvapan, Focetria and Pandemrix (http://www.emea.europa.eu/htms/human/epar/a.htm).