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Human Medicines Research and Development Support Division

Public summary of the evaluation of the proposed paediatric investigation plan

Pandemic live attenuated influenza virus (H5N1) for Prevention of influenza infection

On 10 October 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for pandemic live attenuated influenza virus (H5N1) for the Prevention of influenza infection (EMEA-001559-PIP01-13).

What is Pandemic live attenuated influenza virus (H5N1), and how is it expected to work?

Pandemic live attenuated influenza virus (H5N1) [p/LAIV] is a vaccine that is given as a nasal spray to prevent pandemic influenza (flu). It contains influenza viruses that have been weakened ("attenuated") so that they do not cause disease. Vaccines work by "teaching" the immune system (the body's natural defences) how to defend itself against a disease. When a person is given the vaccine, the immune system recognises the attenuated virus as "foreign" and makes defences against it. The immune system will then be able to respond more quickly when it is exposed to the virus again. This helps to protect against the disease.

p/LAIV is a "pandemic preparedness vaccine" (formerly known as "mock-up" vaccine). This is a special type of vaccine that is designed to help with the management of a future pandemic. A influenza pandemic happens when a new type (strain) of influenza virus appears that can spread easily from person to person because people have no immunity (protection) against it.

Before a pandemic starts, nobody knows which strain of influenza virus will be involved, so pharmaceutical companies cannot prepare the correct vaccine in advance. Instead, they can prepare a vaccine that contains a strain of influenza virus specifically chosen because nobody has been exposed to it, and to which nobody is immune. They can then test this vaccine to see how people react to it, allowing them to predict how people will react when the influenza strain causing the pandemic is included. During a pandemic, the virus strain in p/LAIV will have to be replaced by the strain causing the pandemic before the vaccine can be used.

A similar vaccine containing different strains of attenuated influenza virus is authorised in the European Union in children from 24 months to 18 years of age for the prevention of seasonal influenza (Fluenz and Fluenz Tetra).

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What was the proposal from the applicant?

For children, the applicant proposed:

To study the vaccine in children from 2 years to less than 18 years of age, in a paediatric investigation plan*. The future indication proposed for children is: active immunisation against influenza virus in a pandemic situation. The plan includes a proposal to determine safety and immunogenicity of the vaccine in non-clinical and clinical studies.

The applicant proposed a deferral* for the non-clinical and paediatric clinical studies.

Is there a need to prevent influenza infection in children?

Taking into account the characteristics of the vaccine, the Paediatric Committee considered this vaccine of potential use for the prevention of influenza infection in a pandemic situation. Since an influenza strain causing a pandemic is new, nobody would have any pre-existing immunity against it, and an influenza pandemic can therefore affect all age groups, from infants to the elderly.

What did the Paediatric Committee conclude on the potential use of this medicine in children?

Because there is a need for more vaccines for the prevention of influenza infection in children in a pandemic situation, and this vaccine has a potential interest for children, the Committee considered that non-clinical and clinical studies were necessary.

Due to some safety concerns raised in children below 2 years of age in clinical trials with similar live attenuated vaccines against seasonal influenza and the 2009 H1N1 influenza pandemic, the applicant initially proposed to study the vaccine only in children above 2 years of age. Nevertheless, in children between 12-23 months of age the safety concerns (wheezing) did not result in severe outcomes (such as hospitalisation) and the PDCO considered that in a pandemic situation, the benefit of immunisation may outweigh the risk of wheezing in these children. Therefore the PDCO agreed with the applicant that children from 12-24 months could be included in the clinical trial with caution, after the vaccine has been evaluated in the older age groups.

The Committee agreed with the request of the applicant that the non-clinical and paediatric clinical studies should be deferred because these studies can only be conducted once an influenza pandemic has started and the influenza virus strain causing the pandemic has been made available to the pharmaceutical companies to include it in the vaccine.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in children less than 12 months of age because the vaccine is likely to be unsafe.
- Studies in animals need to be performed, to identify any risk before the vaccine is used in children.
- Once a pandemic has been declared and the virus strain in p/LAIV has been replaced by the strain causing the pandemic, the potential side effects of the vaccine (for example whether it causes fever) will be evaluated in one study. This study will also assess the ability of the vaccine to stimulate an immune response against the virus.

The applicant had originally proposed to compare the vaccine to placebo*; however, the PDCO objected to the use of a placebo group in a vaccine study, particularly in a pandemic situation. Therefore all children participating in the study will receive the vaccine.

- Additional post-marketing studies will be conducted during the pandemic to gather real-time data on the safety and effectiveness of the vaccine. Since these studies are to be conducted post-marketing, they do not fall under the responsibility of the PDCO.

What happens next?

The applicant has now received the EMA Decision* on this medicine. The Decision itself is necessary for the applicant to request in the future a marketing authorisation* for this medicine in adults and/or in children.

The Decision* on the agreed Paediatric Investigation Plan means that the applicant is bound to perform the studies and trials with children as soon as an influenza pandemic has been officially declared. In case of difficulties, or a change in current knowledge or availability of new data, the applicant may request changes to the plan at a later stage. This can be done through a modification of the PIP.

The agreed completion of all the studies and trials included in the Paediatric Investigation Plan is within 17 months after the declaration of an influenza pandemic.

Trials in the Paediatric Investigation Plan will be listed in the public EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/) as soon as they have been authorised to be started, and their results will have to be listed in the register within 6 months after they have completed.

The results of the studies conducted in accordance with the agreed Paediatric Investigation Plan will be assessed, and any relevant information will be included in the Product Information (summary of product characteristics, package leaflet). The product information will also describe which adverse effects are expected with the medicine, and wherever possible, how to prevent or reduce these effects.

*Definitions:

Applicant	The pharmaceutical company or person proposing the Paediatric Investigation Plan or requesting the Product-Specific Waiver
Children	All children, from birth to the day of the 18th birthday.
Paediatric investigation plan (PIP)	Set of studies and measures, usually including clinical studies in children, to evaluate the benefits and the risks of the use of a medicine in children, for a given disease or condition. A PIP may include "partial" waivers (for example, for younger children) and/or a deferral (see below).
Waiver	An exemption from conducting studies in children, for a given disease or condition. This can be granted for all children (product-specific waiver), or in specific subsets (partial waiver): for example, in boys or in children below a given age.
Deferral	The possibility to request marketing authorisation for the use of the medicine in adults, before completing one or more of the studies /measures included in a PIP. The Paediatric Committee may grant a deferral to avoid a delay in the availability of the medicine for adults.
Opinion	The result of the evaluation by the Paediatric Committee of the European Medicines Agency. The opinion may grant a product-specific waiver, or agree a PIP.
Decision	The legal act issued by the European Medicines Agency, which puts into effect the Opinion of the Paediatric Committee.
Pharmaceutical form	The physical aspect of the medicine (the form in which it is presented), for example: a tablet, capsule, powder, solution for injection, etc. A medicine can have more than one pharmaceutical form.
Placebo	A substance that has no therapeutic effect, used as a control in testing new drugs.
Active control	A medicine with therapeutic effect, used as a control in testing new drugs.
Historical control	A group of patients with the same disease, treated in the past and used in a comparison with the patients treated with the new drug.
Route of administration	How a medicine is given to the patient. For example: for oral use, for intramuscular use, for intravenous use, etc. The same medicine, or the same pharmaceutical form, may be given through more than one route of administration.
Patent	A form of protection of intellectual property rights. If a medicinal product is protected by a patent, the patent holder has the sole right to make, use, and sell the product, for a limited period. In certain circumstances, a patent for a medicinal product may be extended for a variable period by a Supplementary Protection Certificate.
Marketing Authorisation	When a Marketing Authorisation is granted, the pharmaceutical company may start selling the medicine in the relevant country (in the whole European Union, if the procedure was a centralised one).