05 July 2016
EMA/258812/2016
Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Human normal immunoglobulin for treatment of primary immunodeficiency

On 29 January 2016 the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for human normal immunoglobulin for the treatment of primary immunodeficiency (EMEA-001797-PIP01-15).

What is human normal immunoglobulin and how is it expected to work?

Human normal immunoglobulin is not authorised in the European Union. Studies in adults and children are currently on-going. This medicine is proposed in adults for the following indications:

- replacement therapy in primary immunodeficiency syndromes with impaired antibody production;
- replacement therapy in hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibodies have failed;
- replacement therapy in hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients (MM) who have failed to respond to pneumococcal immunisation.

This medicine is a highly purified protein extracted from human plasma (part of the blood). It contains immunoglobulin G (IgG), which is a type of antibody. Human normal immunoglobulin has a wide range of activity against organisms that can cause infection. It works by restoring abnormally low IgG levels to their normal range in the patient's blood.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 2 years to less than 18 years of age affected by primary immunodeficiency, in a paediatric investigation plan*. The future indications proposed for children are:

- replacement therapy in primary immunodeficiency syndromes with impaired antibody production;
- replacement therapy in hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibodies have failed;

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- replacement therapy in hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients (MM) who have failed to respond to pneumococcal immunisation.

The plan includes the development of a specific pharmaceutical form to be used in children*, a smaller vial appropriate for the paediatric population from 2 to less than 6 years of age. It also includes a proposal to show efficacy and safety of the medicine in clinical studies.

The applicant proposed a deferral* for the development of a specific pharmaceutical form to be used in children and for the paediatric clinical study.

Is there a need to treat children affected by primary immunodeficiency?

Taking into account the proposed indication in adults, and the characteristics of the medicine, the Paediatric Committee considered this medicine of potential use for the treatment of primary immunodeficiency in children. This condition occurs also in children.

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

At present, some treatments are available for the treatment of primary immunodeficiency in children in the European Union, such as Hizentra that are known to work. The Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from 2 years to less than 18 years of age affected by the condition, and to understand any potential risks.

The Committee considered that there is also a need to develop a specific pharmaceutical form* of this medicine, which would allow to use it safely and accurately in young children, and whose composition* must only include components that are known to be safe in children.

Because there is a need for more medicines for the treatment of primary immunodeficiency in children and this medicine has a potential interest for children, the Committee considered that clinical studies were necessary.

The Committee considered that the clinical development in adults could be finalised before completing the paediatric studies.

The Committee agreed with the request of the applicant that the development of a specific pharmaceutical form to be used in children and the paediatric clinical study should be deferred to avoid a delay in the availability of the medicine for adults.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in children from birth to less than 2 years of age because this medicine does not represent a significant therapeutic benefit over existing treatments for this age group.
- A pharmaceutical form* such as a smaller vial was needed for children from 2 to less than 6 years of age. The new form will be developed by the applicant.
- It is necessary to study if the medicine is effective to treat the primary immunodeficiency in children. This will be done in 1 study to prove that the medicine will prevent occurrence of severe bacterial infections.

- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. The main concern identified by the PDCO is the local tolerability to human normal immunoglobulin.

What happens next?

The applicant has received the EMA Decision (P/0084/2016)* 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 in the next months or years. 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 December 2017.

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). If the medicine proves to be effective and safe to use in children, it can be authorised for paediatric use, with appropriate recommendations on the dose and on necessary precautions. 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).