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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 (CTL019)

On 20 March 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 (CTL019) for the treatment of B lymphoblastic leukaemia/lymphoma (EMA-001654-PIP01-14).

What is CTL019, and how is it expected to work?

This medicine is expected to recognise B cells –cells of the immune system present in abnormally high numbers in B cell leukaemia– via a molecule called CD19, and to specifically attack and destroy them. Cells not carrying CD19 are not recognised nor destroyed by this medicine. CTL019 contains T cells taken from the patient to be treated. These cells express on their surface a protein that associates with CD19.

CTL019 is not authorised in the European Union, for the treatment of B lymphoblastic leukaemia/lymphoma. This medicine is proposed in adults for the treatment of patients with relapsed or refractory B cell acute lymphoblastic leukaemia. Studies in adults and children are currently on-going.

What was the proposal from the applicant?

For children, the applicant proposed to study the medicine in children from 2 years (age at initial B cell leukaemia diagnosis) to less than 18 years of age affected by B cell acute lymphoblastic leukaemia, in a paediatric investigation plan*.

The future indication proposed for children is: treatment of B cell acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed after at least two prior regimens or are refractory.

The plan includes a proposal to show efficacy and safety of the medicine in clinical studies and to develop the medicinal product for children weighing at least 6 kilograms.

The applicant proposed a deferral* for the development of the medicinal product and for its clinical study in children younger than 3 years of age.

Is there a need to treat children affected by B lymphoblastic leukaemia/lymphoma?

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 B lymphoblastic leukaemia/lymphoma since this condition occurs also in children.

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

The Committee considered that the condition is serious enough in children, and that there are no satisfactory treatments available for children yet. At present, some treatments are available for the treatment of B lymphoblastic leukaemia/lymphoma in children in the European Union, such as several chemotherapeutic agents and bone marrow transplantation that are known to work. However there is a need for more medicines for the treatment of B lymphoblastic leukaemia/lymphoma in children.

Since this medicine has a potential interest for children, the Committee considered that clinical studies were necessary. The Committee also considered that new data are required to decide whether the use of this medicine will bring a benefit to children from 6 kilograms of weight to less than 18 years of age affected by the condition, and to understand any potential risks.

The Committee agreed that there is also a need to carry out clinical studies to develop an age appropriate formulation of the medicine, which would allow its efficacious, safe and accurate use in children younger than 3 years of age.

Taking the above into account, the Committee decided that studies with children should start, and some be completed, without waiting for all the results of studies in adults.

The Committee agreed with the request of the applicant that the clinical studies to develop a form of the medicine to be used in very young children should be deferred to avoid a delay in the availability of the medicine for adults and for children between 3 and less than 18 years of age.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- studies are not necessary in children weighing less than 6 kg because the medicinal product cannot be prepared from these children;
- it is necessary to study if the medicine is effective to treat the disease in children. This will be done in 4 clinical studies involving children whose disease is refractory to standard therapy, relapsed after stem cell transplantation (or, in one study are at high risk of relapse) or are ineligible for allogeneic stem cell transplantation.
- 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 potential toxicity of the medicine for the immune system.

What happens next?

The applicant has now received the EMA Decision (P/0103/2015)* 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 2021.

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 18 th 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).