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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Inotuzumab ozogamicin for treatment of acute lymphoblastic leukaemia

On 10 October 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for inotuzumab ozogamicin for the treatment of acute lymphoblastic leukaemia (EMEA-001429-PIP01-13).

What is inotuzumab ozogamicin, and how is it expected to work?

Inotuzumab ozogamicin is not authorised in the European Union. Studies in adults are currently ongoing. This medicine is proposed in adults for the treatment of relapsed or refractory B cell acute lymphoblastic leukaemia.

This medicinal product is formed by two parts: an antibody, which targets the product to specific cells of the immune system (the B cells), and a toxic compound called calichaemicin. The medicine binds to the surface of B cells by associating with a molecule specifically expressed on their surface. It is then internalised and inside the cell calichaemicin causes DNA breaks, which results in cells to committing suicide.

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 CD22-positive B-cell precursor acute lymphoblastic leukaemia or relapsed/refractory CD22-positive B cell malignancies, in a paediatric investigation plan*. The future indication proposed for children is: relapsed or refractory B-cell ALL. The plan includes a proposal to show safety of the medicine in clinical studies and to extrapolate data from studies in adults.

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

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Is there a need to treat children affected by acute lymphoblastic leukaemia?

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 acute lymphoblastic leukaemia. This condition occurs also in children.

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

The Committee agreed with the request of the applicant to be exempt from performing studies in children from birth to less than 1 year, because the Committee concluded that this medicinal product does not seem to have a potential significant benefit over existing treatments for the treatment of acute lymphoblastic leukaemia in this age group.

The Committee came to this conclusion because the paediatric clinical studies with this medicinal product target children with high-risk ALL at their first relapse, which is rare before 1 year of age.

At present, some treatments are available for the treatment of acute lymphoblastic leukaemia in children in the European Union, such as several chemotherapeutic agents and hematopoietic stem cell transplantation, which are known to work. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from 1 year to less than 18 years affected by the condition, and to understand any potential risks.

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

The Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults, before starting the paediatric studies.

The Committee agreed with the request of the applicant that the paediatric clinical studies should be deferred because of the potential toxicity associated with this medicinal product.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Determination of the best dose should be done with 1 trial of the medicine's behaviour in the body, which should also establish how the body reacts to the medicine.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in 1 study comparing the medicine to active control*.
- 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 liver and for the bone marrow.

What happens next?

The applicant has now received the EMA Decision (P/0304/2014)* 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 2023.

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 start, 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

*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).