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Human Medicines Research and Development Support Division

Summary of the evaluation of the proposed paediatric investigation plan

Recombinant soluble fusion protein with a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain (ACE-536) for treatment of myelodysplastic syndromes and treatment of beta-thalassaemia.

On 15 August 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for ACE-536 for the treatment of myelodysplastic syndromes and the treatment of beta-thalassaemia (EMEA-001521-PIP01-13).

What is ACE-536, and how is it expected to work?

ACE-526 is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the treatment of anaemia in patients with myelodysplastic syndromes and for the treatment of anaemia in patients with beta-thalassemia.

This medicine is expected to increase the number of mature red blood cells thus increasing the amount of functional haemoglobin, a molecule transporting oxygen. This, in turn, will lead to increased levels of oxygen been available in the 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 beta-thalassaemia intermedia and major, in a paediatric investigation plan*. The future indication proposed for children is: treatment of anaemia in patients with beta-thalassemia. The plan included a proposal to determine the right dose and to show efficacy and safety of the medicine in non-clinical and clinical studies.

Is there a need to treat children affected by myelodysplastic syndromes and by beta-thalassaemia?

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 beta-thalassaemia. 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 being exempted from performing studies in children with myelodysplastic syndromes, because the Committee concluded that this medicinal product does not seem to have a potential significant benefit over existing treatments for the condition.

The Committee came to this conclusion because myelodysplastic syndromes are different in adults and in children and the mechanism of action of this medicinal product is predicted to be of limited utility in these paediatric diseases.

At present, some treatments are available for the treatment of beta-thalassaemia in children in the European Union, such as blood transfusions, chelation therapy, bone marrow transplant and cord blood transfusion; other treatments, such as gene therapy, are under study. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to the children 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 to be delivered with an administration device, which would allow to use the medicine 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 beta-thalassaemia in children, and this medicine has a potential interest for children, the Committee considered that non-clinical and 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.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in children from birth to 6 months of age with beta-thalassaemia because in these children foetal haemoglobin is normally still present and compensates for the defective adult haemoglobin, which is responsible for the disease.
- An age-appropriate pharmaceutical form for subcutaneous use will be developed by the applicant.
- Studies in models of the disease need to be performed, to determine how to best study / use the medicine in children.
- Determination of the best dose should be made in one trial by studying the medicine's behaviour in the body and the body's reactions to the medicine.>
- It is necessary to study if the medicine is efficacious to treat the disease in children. This will be done in two studies comparing the medicine to placebo (although patients during the studies will receive standard treatments).
- 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 caused by antibodies generated against the medicine.

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 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 June 2019.

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 efficacious 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.
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).