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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Recombinant human heparan N-sulfatase (rhHNS) for the treatment of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A)

On 12 December 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for recombinant human heparan N-sulfatase (rhHNS) for the treatment of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A) (EMEA-001634-PIP01-14).

What is recombinant human heparan N-sulfatase (rhHNS), and how is it expected to work?

Recombinant human heparan N-sulfatase (rhHNS) is not authorised in the European Union. Since this medicinal product is intended for a paediatric disease, studies in adults were not conducted and studies in children are currently on-going. This medicine is proposed for the treatment of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A).

This medicine is expected to replace the defective human heparan N-sulfatase (a protein required for correct processing of long chains of sugar molecules in cells) in patients with the disease.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from birth to less than 18 years of age affected by mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A), in a paediatric investigation plan*. The future indication proposed for children is: Long term intrathecal (IT) enzyme replacement therapy (ERT) in patients in early stage mucopolysaccharidosis IIIA disease or mild cognitive impairment as a result of the disease. The plan includes 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 mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A)?

Taking into account the characteristics of medicine, the Paediatric Committee considered this medicine of potential use for the mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A). This condition occurs almost exclusively in children.

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

At present, no treatment is authorised for mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A) for children in the European Union. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from birth 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 mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A) in children, and this medicine has a potential interest for children, the Committee considered that non-clinical and clinical studies were necessary.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- As mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A) affects neonates, 1 clinical study including children from birth to less than 3 months of age will be performed to obtain the necessary data.
- Studies in animals need to be performed, to identify any risk before the medicine is used in infants and neonates / young children.
- Determination of the best dose should be done with 2 trials.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in 2 studies comparing the medicine to historical control* or to patients with the disease that were not treated.
- 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 generation of antibodies against the medicine as well as safety issues related to the device used to inject the medicine in the central nervous system.

What happens next?

The applicant has now received the EMA Decision (P/0027/2015)* on this medicine. The Decision itself is necessary for the applicant to request in the future a marketing authorisation* for this medicine 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 April 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 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).