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Public summary of the evaluation of a proposed paediatric investigation plan

Simtuzumab for treatment of hepatic fibrosis and hepatic cirrhosis

On 20 March 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for simtuzumab for the treatment of hepatic fibrosis and hepatic cirrhosis (EMA-001511-PIP02-13).

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

Simtuzumab (SIM) is a recombinant humanised monoclonal antibody directed against an enzyme involved in the development of pathologic fibrotic tissue. By inhibiting this enzyme this medicine is expected to inhibit formation of pathologic connective tissue in liver fibrosis.

Simtuzumab is not currently authorised in the European Union. This medicine is proposed in adults for the prevention of progression of liver fibrosis in patients with nonalcoholic steatohepatitis (NASH) and the prevention of progression of liver fibrosis in patients with primary sclerosing cholangitis (PSC). Clinical studies in adults are currently on-going.

What was the proposal from the applicant?

For children, the applicant proposed to study the medicine in children from 12 to less than 18 years of age affected by hepatic fibrosis and cirrhosis, in a paediatric investigation plan*.

The future indication proposed for children is treatment of advanced hepatic fibrosis or cirrhosis. The plan includes a clinical study to determine the right dose and show safety and efficacy of the medicine.

The applicant proposed a deferral* for this paediatric clinical study.

Is there a need to treat children affected by hepatic fibrosis and cirrhosis?

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 hepatic fibrosis and hepatic cirrhosis. These conditions occur also in children.



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

At present, no pharmacological treatment is authorised for the treatment of progressive hepatic fibrosis and cirrhosis in 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 28 days 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 strength of the pharmaceutical form* of this medicine, 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.

The Committee considered that the conditions are serious enough in children, and that there are no treatments available for children yet. Consequently, studies with children should start without waiting for all the results of studies in adults.

The Committee agreed with the request of the applicant that the completion of the development of a specific pharmaceutical form to be used in children and of 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 were not necessary in children from birth to less than 28 days of age because liver fibrosis at that age generally requires surgical intervention.
- A specific strength of the solution for injection was needed for children in order to enable suitable injection volumes for children as young as 1 month of age.
- Studies in animals need to be performed, to identify any risk before the medicine is used in infants and neonates / young children.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in one study.
- Partial extrapolation of efficacy between adults and children, is considered possible in the development of this product, because even though the aetiology of liver fibrosis/cirrhosis in children may be very different from the aetiology in adult subjects, the underlying mechanism that leads to liver fibrosis/cirrhosis is expected to be similar in adults and children.

What happens next?

The applicant has now received the EMA Decision (P/0096/2015)* 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 September 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).