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Human Medicines Research and Development Support Division

Public summary of the evaluation of the proposed paediatric investigation plan

Clostridium difficile toxin B human monoclonal antibody for treatment of Clostridium difficile infection

On 14 November 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for Clostridium difficile toxin B human monoclonal antibody for the treatment of Clostridium difficile infection (EMA-001645-PIP01-14).

What is Clostridium difficile toxin B human monoclonal antibody, and how is it expected to work?

Clostridium difficile toxin B human monoclonal antibody is not authorised in the European Union, but studies in adults are currently on-going. This medicine is proposed in adults for the prevention of recurrence of Clostridium difficile infection related diarrhoea.

This medicine is expected to neutralise a toxin (toxin B), produced by Clostridium difficile bacteria in the digestive system. By doing so, it is expected that this medicine can reduce the recurrence of diarrhoea caused by the bacteria.

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 Clostridium difficile infection in a paediatric investigation plan*. The future indication proposed for children is: Prevention of recurrence of Clostridium difficile infection related diarrhoea. The plan includes a proposal to determine the right dose and to show efficacy and safety of the medicine in clinical studies.

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

Is there a need to treat children affected by Clostridium difficile infection?

Taking into account the proposed indication in adults, and the characteristics of the medicine, the Paediatric Committee considered this medicine of potential use for treatment of Clostridium difficile infection. This condition occurs also in neonates, infants and toddlers, children and adolescents.

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

At present, some treatments are available for *Clostridium difficile* infection in children in the European Union, such as metronidazole or vancomycin that are known to work. However, despite high initial response rates, the recurrence rate of diarrhoea is high with either drug. 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 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 vial size for this medicine, which would allow using the medicine safely and accurately in young children.

Because there is a need for more medicines for the treatment of *Clostridium difficile* infection in children, and this medicine has a potential interest for children, the Committee considered that clinical studies, in combination with a modelling and simulation study were necessary.

The Committee agreed with the request of the applicant that the development of a specific vial size to be used in children and paediatric clinical studies 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:

- As *Clostridium difficile* infection affects neonates, 1 clinical study including children from birth to less than 2 years of age should be performed to obtain the necessary data.
- A smaller vial size is needed for children aged from birth to less than 2 years of age.
- Determination of the best dose should be done with 2 clinical trials of the medicine's behaviour in the body in combination with a modelling & simulation study.
- It is necessary to study if the medicine is efficacious to treat the disease in children. This will be done in 1 study comparing the medicine to placebo* in children from 2 years of age.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. This will be done in 2 paediatric clinical studies.

What happens next?

The applicant has now received the EMA Decision* (P/0340/2014) 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 November 2020.

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 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).