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Human Medicines Research and Development Support Division

Summary of the evaluation of the proposed paediatric investigation plan

N-[(1,3-dicyclohexyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)carbonyl]glycine for treatment of anaemia due to chronic disorders

On 20 June 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for N-[(1,3-dicyclohexyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)carbonyl]glycine for treatment of anaemia due to chronic disorders (EMEA-001452-PIP01-13).

What is N-[(1,3-dicyclohexyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)carbonyl]glycine, and how is it expected to work?

N-[(1,3-dicyclohexyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)carbonyl]glycine 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 associated with chronic renal disease.

This medicine is expected to stimulate the production of red blood cells and increase the haemoglobin concentration through the inhibition of certain enzymes in patients with anaemia, who suffer from a decrease in the number of red blood cells or less than the normal quantity of haemoglobin in the blood.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 2 to 17 years of age affected by anaemia due to chronic kidney disease, in a paediatric investigation plan*. The future indication proposed for children is: Treatment of anaemia associated with chronic kidney disease. The plan includes the development of a specific pharmaceutical form to be used in children*, i.e. an oral solution or oral suspension. It also includes a proposal to determine the right dose and to show efficacy and safety of the medicine in non-clinical and clinical studies and to extrapolate data from studies in adults.

Is there a need to treat children affected by a similar disease?

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 anaemia due to

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chronic disorders. This condition occurs also in children. The Paediatric Committee concluded that the highest need for children in this condition would be for those children with anaemia associated with chronic kidney disease.

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

At present, some treatments are available for the treatment of anaemia due to chronic disorders in children in the European Union, such as erythropoetins (medicines that stimulate the production of red blood cells). 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, which would allow to use the medicine safely and accurately in young children (oral solution or oral suspension), 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 anaemia due to chronic disorders 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 clinical paediatric studies.

Studies with children will be done between 2020 and 2027.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in some groups of children because of safety concerns in children below 1 year of age due to the specific metabolism of this medicine.
- A pharmaceutical form* such as an oral solution or suspension was needed for children aged from 1 to 17 years. An oral solution or suspension will be developed by the applicant.
- Determination of the best dose should be made with 2 studies of the medicine's behaviour in the body.
- It is necessary to show efficacy to treat the disease in children. This will be done in 2 studies comparing the medicine to active controls.
- Partial extrapolation of efficacy is possible in the development of this product, between adults and children, because data suggest that the enzymatic pathway on which this medicine acts functions in a similar manner in adults and children. It is therefore expected that this medicine will have similar efficacy to that observed in adults.

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 will perform the studies and trials 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 January 2027.

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).