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Public summary of the evaluation of the proposed paediatric investigation plan Glucagon for treatment of hypoglycaemia

On 19 June 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for glucagon for the treatment of hypoglycaemia(EMA-001657-PIP01-14).

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

Glucagon is a polypeptide hormone which causes conversion of stored hepatic glycogen into glucose, which is released into the bloodstream. Therefore, this medicine is expected to raise blood glucose levels.

Glucagon based medicines are currently authorised in adults and children as powder and solvent for solution for injection for the treatment of severe hypoglycaemic reactions, which may occur in the management of insulin treated persons with diabetes mellitus.

What was the proposal from the applicant?

The applicant proposed to study the medicine in children from 2 years to less than 18 years of age with diabetes receiving insulin therapy that are affected by hypoglycaemia, in a paediatric investigation plan*. The future indication proposed for children was: treatment of severe hypoglycaemia in insulin-treated children. The plan included the development of a specific pharmaceutical form to be used in children* which was nasal powder. The plan also included a proposal to determine the right dose in the paediatric population and to show safety of the medicine in clinical studies and how to extrapolate data from studies in older children and adults to younger ones.

The applicant proposed a deferral* for the development of a specific pharmaceutical form to be used in children and for paediatric clinical studies.

Is there a need to treat children affected by hypoglycaemia?

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 hypoglycaemia of any cause in children. The committee did not agree to restrict the condition only to the treatment of hypoglycaemia in people with diabetes receiving insulin therapy.



Based on existing knowledge, and on data submitted by the Applicant, the Paediatric Committee concluded that the scope of the PIP should more broadly target hypoglycaemia irrespective of the cause. The Committee concluded that hypoglycaemia does affect children, and the product could potentially address a paediatric need in this condition. It was agreed that the easier, and pain free route of administration (a puff in the nose as compared to subcutaneous or intramuscular injection) and a potentially better gastro-intestinal safety profile could represent a significant therapeutic benefit in the paediatric population over existing treatments.

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 hypoglycaemia in children in the European Union. While mild hypoglycaemia is generally easily treated by the oral consumption of carbohydrates, in severe hypoglycaemia the patient may require glucagon, which is available as intravenous solution or for intramuscular or subcutaneous injection. The Committee considered that there is a need to develop a nasal powder, 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 new data are required to decide whether the use of glucagon nasal powder will bring a benefit over existing glucagon formulations to children from 1 to less than 18 years of age affected by the condition, and to understand any potential risks and that clinical studies were necessary.

The Committee agreed with the request of the applicant that the development of the medicine to be used in children below 4 years of age and paediatric clinical studies in this age group 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 are not necessary in children from birth to less than 1 year of age because there is no expected significant therapeutic benefit over existing treatments (e.g. glucagon infusion) in this age group.
- A dosing device for the nasal powder was needed for children aged from 1 to less than 18 years of age and will be developed by the applicant.
- Determination of the best dose should be done with 3 trials of the medicine's behaviour in the body and the body's reactions to it.
- It is necessary to study if the medicine is effective and easy to use for the treatment of the disease in children. This will be done in one study.
- Extrapolation of efficacy is possible in the development of this product, between adults and children, because similar efficacy is expected if the medicine's behaviour in the body as well as the body's reactions to it can be shown to be similar in children and 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 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 December 2026.

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).