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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Osilodrostat for the treatment of adrenal cortical hyperfunction

On 11 December 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for osilodrostat for the treatment of adrenal cortical hyperfunction (EMA-000315-PIP02-15).

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

Osilodrostat is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the Treatment of hypercortisolism (Cushing's syndrome) of endogenous origin.

This medicine is expected to reduce the excessive production of two hormones, cortisol and aldosterone, that occurs in Cushing's disease or other similar situations. The two hormones are produced normally by the two adrenal glands, but in rare cases the production can be excessive for various reasons. Osilodrostat acts by blocking the action of specific substances, called enzymes that speed up the production of cortisol and aldosterone.

What was the proposal from the applicant?

For children, the applicant proposed:

- Not to do any study in children from birth to less than 6 years of age, because the condition is exceedingly rare in this age group, and because the medicine would likely be unsafe in younger children. Therefore, the applicant requested an exemption (waiver*) from the obligation to study the medicine in this age group.
- To study the medicine in children from 6 to less than 18 of age affected by adrenal cortical hyperfunction, in a paediatric investigation plan*. The future indication proposed for children is: Treatment of Cushing's disease in adolescents and children aged 6 years and older for whom pituitary surgery is not an option or for whom surgery has failed. The plan includes a proposal to determine the right dose and to show the activity of the medicine in non-clinical and clinical studies, and to extrapolate data from studies in adults.

The applicant proposed a deferral* for the non-clinical studies and the paediatric clinical study.

Is there a need to treat children affected by adrenal cortical hyperfunction?

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 adrenal cortical hyperfunction. This condition occurs also in children, albeit rarely.

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

The Committee agreed with the request of the applicant to be exempt from performing studies in children from birth to less than 6 years of age, because the condition for which the medicinal product could potentially be used is exceedingly rare in these children, and studies in this age group are not likely to be feasible. The Committee also concluded that this medicinal product is likely to be not safe for the treatment of adrenal cortical hyperfunction in younger children.

The Committee came to this conclusion because the condition is exceedingly rare before the age of 6, and when it does occur it is amenable to surgical cure. Regarding the safety, younger children may be more predisposed to gastrointestinal disturbances and the resulting fluid and electrolyte abnormalities.

At present, some treatments are available for the treatment of adrenal cortical hyperfunction in children in the European Union, such as metopirone, mitotane and ketoconazole. Nevertheless, the Committee considered that new data are required to decide whether the use of this new medicine will bring a significant benefit to children from 6 to less than 18 years, affected by the condition, and to understand any potential risks.

Because there is a need for more medicines for this condition 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 the condition is serious enough in children, and consequently, studies with children should start immediately after the results of studies in adults become available.

The Committee agreed with the request of the applicant that completion of the clinical study should be deferred to avoid a delay in the availability of the medicine for adults, because the paediatric study will take longer to complete and can only be initiated after results from studies in adult patients are available.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in children below the age of 6 years of age, because the medicine is likely to be unsafe and because studies are believed to be unfeasible.
- Studies in juvenile animals need to be performed, to identify any risk before the medicine is used in children.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in 1 study evaluating the behaviour of the medicine and its effect to the function of the adrenal gland.

- Partial extrapolation of efficacy is possible in the development of this product, between adults and children, because supporting data will be available from a modelling and simulation study, and the course of the disease and response to treatment are expected to be similar in children and in adults.

What happens next?

The applicant has received the EMA Decision (P/0011/2016)* 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 June 2022.

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.

Subsequent modifications of the agreed Paediatric Investigation Plan

N/A

*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).