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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Valaciclovir (hydrochloride) for treatment and prevention of Herpes simplex virus disease and treatment and prevention of Varicella Zoster virus disease

On 20 June 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for Valaciclovir (hydrochloride) for the treatment and prevention of Herpes simplex virus disease and treatment and prevention of Varicella Zoster virus disease (EMEA-001548-PIP01-13).

What is Valaciclovir (hydrochloride), and how is it expected to work?

Valaciclovir (hydrochloride) is a medicine authorised currently in adults and children from 12 years of age for:

- Varicella zoster virus (VZV) infections – herpes zoster: Valtrex is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults. Valtrex is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression.
- Herpes simplex virus (HSV) infections: Valtrex is indicated for the treatment and suppression of HSV infections of the skin and mucous membranes including:
  - treatment of first-episode of genital herpes in immunocompetent adults and adolescents and in immunocompromised adults
  - treatment of recurrences of genital herpes in immunocompetent adults and adolescents, and in immunocompromised adults
  - suppression of recurrent genital herpes in immunocompetent adults and adolescents and in immunocompromised adults
- Treatment and suppression of recurrent ocular HSV infections in immunocompetent adults and adolescents and in immunocompromised adults
- Cytomegalovirus (CMV) infections: Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents

This medicine has antiviral activity against HSV types 1 (HSV-1) and 2 (HSV-2) and VZV and therefore could treat infections caused by these viruses.

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What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 1 month to less than 18 years of age, affected by Herpes simplex virus disease and by Varicella Zoster virus disease in a paediatric investigation plan*.

The future indications proposed for children are:

Treatment and prevention of Herpes simplex virus disease of the skin and mucous membranes

Treatment and prevention of recurrent genital herpes

Treatment and prevention of recurrent ocular Herpes simplex virus disease

The plan includes the development of a specific pharmaceutical form to be used in children* powder for oral suspension. It also includes a proposal to determine the right dose and to show efficacy and safety of the medicine in clinical studies.

Is there a need to treat children affected by Herpes simplex virus disease and Varicella Zoster virus 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 and prevention of Herpes simplex virus disease and treatment and prevention of Varicella Zoster virus disease. Thess conditions occur also in children.

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

At present, some treatments are available for the treatment and prevention of Herpes simplex virus disease and treatment and prevention of Varicella Zoster virus disease in children in the European Union, such as Valtrex that are known to work. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from 1 month to less than 18 years 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, and whose composition* must only include components that are known to be safe in children.

Because there is a need for more medicines for treatment and prevention Herpes simplex virus disease and for treatment and prevention of Varicella Zoster virus disease in children, and this medicine has a potential interest for children, the Committee considered that clinical studies were necessary.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in neonates because the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.
- A pharmaceutical form* such as powder for oral suspension was needed for children aged from 1 month to less than 18 years of age. The powder for oral suspension will be developed by the applicant.

- Determination of the best dose should be done with two trials of the medicine's behaviour in the body and the body's reactions to it.
- Partial extrapolation of efficacy is possible in the development of this product, between adults and younger children, because valacyclovir is already authorised and its efficacy has been already demonstrated.

What happens next?

The applicant has now received the EMA Decision (P/0207/2014)* on this medicine. The Decision itself is necessary for the applicant to request a new indication, a new route of administration* or a new pharmaceutical form*, as this medicine is already authorised and protected by a patent*.

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 <e.g. September 2017.

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 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.
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).