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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Letermovir for the prevention of cytomegalovirus infection

On 22 May 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for letermovir for the prevention of cytomegalovirus (CMV) infection (EMEA-001631-PIP01-14).

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

Letermovir is thought to block the action of an enzyme of the virus called 'terminase', which is involved in packaging the correct length DNA in the protein shells of the citomegalovirus (CMV). By blocking the enzyme, letermovir is expected to prevent viruses from reaching maturity, so that no new infectious viruses can be produced. CMV is a common virus that normally causes a mild infection such as a sore throat but in people with weakened immunity, such as transplant patients receiving immunosuppressant treatment, CMV can become active again and cause severe infection.

This medicine is proposed in adults for the 'prevention of CMV viraemia and/or disease in at-risk patients having undergone an allogeneic haematopoietic stem cell transplant' and the 'prevention of CMV viraemia and/or disease in at-risk patients having undergone a solid organ transplant'. Letermovir is not authorised in the European Union. Studies in adults are currently on-going.

What was the proposal from the applicant?

The applicant proposed to study the medicine in children from birth to less than 18 years of age who have received a haematopoietic stem cell transplant or solid organ transplant, in a paediatric investigation plan*. These children are at risk of CMV infection due to the immunosuppressant treatment they are receiving. The future indication proposed for children is: 'prevention of CMV viraemia and/or disease in paediatric transplant recipients'. The plan includes the development of three pharmaceutical forms to be used in children* (a lower strength film-coated tablet, granules and concentrate for solution for infusion). It also includes a proposal to determine the right dose and to show safety of the medicine in a clinical study in children who have received a haematopoietic stem cell transplant. The plan also proposed to extrapolate data from studies in children and adults who have received a haematopoietic stem cell transplant and adults who have received a solid organ transplant to children who have received a solid organ transplant.

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The applicant proposed a deferral* for the development of the specific pharmaceutical forms to be used in children, for the clinical studies and for the extrapolation and modelling & simulation studies.

Is there a need to treat children affected at risk of CMV 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 the prevention of CMV infection. Solid organ and haematopoietic stem cell transplants are also performed in children of all ages, and like adults, these children can be at risk of CMV infection due to the immunosuppressant treatment they are receiving to prevent graft rejection.

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

At present, no treatment is authorised for the prevention of CMV infection in children who have received a haematopoietic stem cell transplant.

Some treatments are available for the prevention of CMV infection in recipients of solid organ transplants, such as ganciclovir and valganciclovir. However, letermovir has a different mechanism of action to current treatments, which may bring improved tolerability and effectiveness against strains of cytomegalovirus resistant to existing antiviral medicines.

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 who are at risk of CMV infection.

The Committee considered that there is also a need to develop specific pharmaceutical forms* 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.

The Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults before starting the paediatric studies and agreed with the request of the applicant that the development of the specific pharmaceutical forms to be used in children, the clinical studies, the extrapolation study and the modelling & simulation study should be deferred.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Pharmaceutical forms* were needed for children aged from birth to less than 18 years of age.
- Determination of the best dose should be done with a trial of the medicine's behaviour in the body.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. Safety and tolerability will be monitored in the clinical study.
- The clinical study will also evaluate if the medicine is effective at preventing CMV viraemia and/or disease in children.
- As solid organ and haematopoietic stem cell transplants are sometimes performed also in neonates, the clinical study will include children from birth.
- The clinical study will be performed in children who have received a haematopoietic stem cell transplant. Modelling & simulation and extrapolation will be used to address children who have received a solid organ transplant.

What happens next?

The applicant has now received the EMA Decision (P/0155/2015)* 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 August 2023.

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).