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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Emtricitabine / rilpivirine / tenofovir alafenamide for the treatment of human immunodeficiency virus (HIV-1) infection

On 17 April 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for emtricitabine / rilpivirine / tenofovir alafenamide for the treatment of human immunodeficiency virus (HIV-1) infection (EMEA-001679-PIP01-14).

What is emtricitabine / rilpivirine / tenofovir alafenamide and how is it expected to work?

Emtricitabine / rilpivirine / tenofovir alafenamide is a 'fixed-dose combination', meaning it contains three active substances: emtricitabine, which is a nucleoside reverse transcriptase inhibitor (NRTI); rilpivirine, which is a non-nucleoside reverse-transcriptase inhibitor (NNRTI); and tenofovir alafenamide, which is a second generation 'prodrug' of tenofovir, meaning that it is converted in the body into the active substance tenofovir, a nucleotide reverse transcriptase inhibitor (N[t]RTI).

All three active substances block the activity of reverse transcriptase, an enzyme produced by HIV that allows it to infect cells and make more viruses. By blocking this enzyme emtricitabine / rilpivirine / tenofovir alafenamide keeps the amount of HIV in the blood at a low level.

Emtricitabine on its own has already been approved in the European Union (EU) as Emtriva since 2003. A first generation prodrug of tenofovir, tenofovir disoproxil fumarate, has been approved as Viread since 2002. Rilpivirine has been approved since 2011 as Edurant. A combination of emtricitabine, rilpivirine and tenofovir disoproxil has been approved as Eviplera since 2011.

The combination emtricitabine / rilpivirine / tenofovir alafenamide is not authorised in the European Union and studies in adults are currently on-going. This medicine is proposed in adults for the treatment of human immunodeficiency virus (HIV-1) infection.

What was the proposal from the applicant?

For children, the applicant proposed to evaluate the medicine for use in children from 6 years to less than 18 years of age affected by HIV-1 infection, as part of a paediatric investigation plan*. The future indication proposed for children is treatment of HIV-1 infection.

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In the paediatric investigation plan the same adult formulation was planned to be used in children and adolescents. The plan included a proposal to show that the tablet containing all three substances is absorbed in the body in the same way as the separate tablets given concurrently under similar conditions in healthy adult volunteers. A proposal to extrapolate efficacy assumptions for the emtricitabine / rilpivirine / tenofovir alafenamide fixed-dose combination to the paediatric population from 6 to less than 12 years of age was also included.

The applicant proposed a deferral* for the extrapolation study.

Is there a need to treat children affected by HIV-1 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 treatment of human immunodeficiency virus (HIV-1) infection. This condition occurs also in children, who can be infected from their mothers at birth. In addition, like adults, adolescents can become infected with HIV e.g. through sexual transmission or through contaminated needles for injection drug use.

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

At present, several treatments are available for the treatment of HIV-1 infection in children in the European Union. These include several other NRTIs and NNRTIs, but these are not authorised for children and adolescents in single-tablet regimens. The PDCO considered that the added convenience of having to take only a single tablet per day (or a single dose of an age-appropriate pharmaceutical form per day, respectively) was highly relevant to children of all ages just as for adults.

The Committee considered that there was 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 emtricitabine / tenofovir alafenamide (as a two-component fixed-dose combination and as part of other fixed-dose combinations) and rilpivirine are already being studied separately in children, the Committee considered that clinical studies in children with the emtricitabine / rilpivirine / tenofovir alafenamide fixed-dose combination were not necessary.

The Committee agreed with the request of the applicant that the development of a specific pharmaceutical form to be used in children should be deferred. Furthermore the completion of the clinical study in healthy adult volunteers to compare the age-appropriate oral formulation with the adult film-coated tablet - should also be deferred, because the doses of emtricitabine / tenofovir alafenamide and of rilpivirine that are safe and effective in children need first be confirmed in the ongoing paediatric studies with the individual components.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Development of emtricitabine / rilpivirine / tenofovir alafenamide is not required for newborn infants less than 4 weeks of age, since - due to the low sensitivity of HIV testing at birth and the need for a repeat test to confirm HIV-infection -treatment with emtricitabine / rilpivirine / tenofovir alafenamide is unlikely to start before 4 weeks of age in clinical practice.
- A age-appropriate pharmaceutical form* was needed for children aged from 4 weeks to less than 12 years of age. Tablets of an appropriate strength and size, and an oral formulation for the

youngest children and those not able to swallow tablets will be developed by the applicant. The applicant will also conduct a clinical study in healthy adult volunteers to compare the age-appropriate oral formulation with the adult film-coated tablet.

- Additional studies are not necessary in children because studies to determine the dose and to determine safety and efficacy in children are already being conducted with the individual components, rilpivirine and emtricitabine / tenofovir alafenamide.

What happens next?

The applicant has now received the EMA Decision (P/0107/2015)* 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 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 2021.

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).