EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 March 2015
EMA/793626/2014
Human Medicines Research and Development Support Division

Summary of the evaluation of the proposed paediatric investigation plan

Emtricitabine / Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin- 9-yl)propan-2-yl]-oxy}methyl)(phenoxy) phosphoryl]-Lalaninate, (2E)-but-2-enedioate (2:1) (thereafter referred to as emtricitabine / tenofovir alafenamide) for treatment of human immunodeficiency virus (HIV-1) infection

On 16 January, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for emtricitabine / tenofovir alafenamide for the treatment of HIV-1 infection (EMEA-001577-PIP02-14).

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

Emtricitabine / tenofovir alafenamide is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral (ARV) agents.

Emtricitabine / tenofovir alafenamide is a 'fixed-dose combination', meaning it contains two active substances: emtricitabine, which is a nucleoside reverse transcriptase inhibitor (NRTI); and tenofovir alafenamide, which is a 2nd generation 'prodrug' of tenofovir, meaning that it is converted into the active substance tenofovir in the body. Tenofovir is a nucleotide reverse transcriptase inhibitor (NRTI). Both active substances block the activity of reverse transcriptase, an enzyme produced by HIV that allows it to infect cells and produce more viruses. Emtricitabine / tenofovir alafenamide, when taken in combination with other ARV agents, keeps the amount of HIV in the blood at a low level. It does not cure HIV infection or AIDS, but it may delay the damage to the immune system and the development of infections and diseases associated with AIDS.

Emtricitabine on its own has already been approved in the European Union (EU) as Emtriva since 2003. A 1st generation prodrug of tenofovir, tenofovir disoproxil fumarate, has been approved as Viread since 2002. A combination of tenofovir disoproxil and emtricitabine has been approved as Truvada since 2005.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 4 weeks to 18 years of age affected by HIV-1 infection, in a paediatric investigation plan*. The future indication proposed for children is: treatment of HIV-1 infection in combination with other ARV agents. The plan includes the development of specific pharmaceutical forms to be used in children*. It also includes a proposal to determine the right dose and to show efficacy and safety of the medicine in clinical studies, as well as a proposal to use modelling & simulation and extrapolation to address children who are failing their current ARV regimen.

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 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 injection needles.

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

At present, some therapies are available for the treatment of HIV-1 infection in children in the European Union. These include several other NRTIs, although not all of these are available as fixed-dose combinations, and some are only authorised above a certain weight cut-off, or have more inconvenient dosing compared to emtricitabine / tenofovir alafenamide.

Therefore, the Committee considered that new data are required to decide whether the use of the emtricitabine / tenofovir alafenamide fixed-dose combination will bring a benefit to the children affected by HIV-1 infection, 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 the treatment of HIV-1 infection in children, and this medicine has a potential interest for children, the Committee considered that clinical studies were necessary.

The Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults, before starting the paediatric studies.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in newborn infants less than 4 weeks of age due to the low sensitivity of HIV testing at birth and the need for a repeat test to confirm HIV-infection. In clinical practice treatment with emtricitabine / tenofovir alafenamide is unlikely to start before 4 weeks of age.
- A pharmaceutical form* was needed for children aged from 4 weeks to 12 years of age. Film-coated tablets of an appropriate strength and size, and an age-appropriate oral dosage form for the youngest children 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. The 'best dose' in children is the dose producing the same level of drug as the level that has been shown to be safe and effective against the virus in adults. It is generally expected that a medicine will then also be effective against the virus in children.
- It is necessary to study if the medicine is efficacious to treat the disease in children. The two trials will also assess the ability of emtricitabine / tenofovir alafenamide to suppress HIV replication and delay the damage to the immune system.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. The main concern identified by the PDCO is the potential toxicity of the medicine to the kidney and bone.
- The clinical studies will be performed in children who are virologically suppressed on their current regimen (or treatment-naïve in the youngest age group). Modelling & simulation and extrapolation will be used to address children who are failing their current regimen.

What happens next?

The applicant has now received the EMA Decision (P/0032/2015)* 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 March 2020.

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 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.
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).