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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Emtricitabine / tenofovir disoproxil fumarate (Truvada) for the treatment of human immunodeficiency virus (HIV-1) infection and for the prevention of human immunodeficiency virus (HIV-1) infection

On 13 November 2015 the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for emtricitabine / tenofovir disoproxil fumarate (Truvada) for the treatment of human immunodeficiency virus (HIV-1) infection and for the prevention of human immunodeficiency virus (HIV-1) infection (EMEA-001091-PIP02-15).

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

Truvada is a medicine that in the European Union (EU) has been authorised in adults for the antiretroviral combination therapy for the treatment of HIV-1 infection since 2005.

Truvada is now being developed in adults in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

Truvada is a fixed-dose combination, meaning it contains two active substances: emtricitabine, which is a nucleoside reverse transcriptase inhibitor (NRTI); and tenofovir disoproxil, which is a 'prodrug' of tenofovir. This means that it is converted into tenofovir in the body. Tenofovir is a nucleotide reverse transcriptase inhibitor (NRTI). Both emtricitabine and tenofovir work in similar ways by blocking the activity of reverse transcriptase, an enzyme produced by HIV that allows it to infect cells and make more viruses.

Truvada is not currently authorised in children or adolescents in the EU. However, both active substances are individually authorised in the EU in children and adolescents: emtricitabine (as Emtriva) from 4 months of age and tenofovir disoproxil fumarate (as Viread) from 2 years of age.

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What was the proposal from the applicant?

For the treatment of HIV-1 infection, the applicant proposed to use the adult tablet in adolescents. The plan therefore only included a completed study in healthy adult volunteers, which showed that the tablet containing both substances is absorbed in the body in the same way as the separate tablets given concurrently under similar conditions, and which formed the basis for the approval of Truvada in adults. The future indication proposed for children is: 'Treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to 18 years.'

For the prevention of HIV-1 infection, the applicant also proposed to use the adult tablet in adolescents. The plan therefore only included an extrapolation study to support the use of Truvada as PrEP in adolescents based on data from PrEP in adults and from the use of both active substances in the treatment of HIV-1 infection in adolescents. The future indication proposed for children is: 'In combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adolescents aged 12 to 18 years at high risk'.

The applicant proposed a deferral* for the extrapolation study.

Is there a need to treat children affected by HIV-1 infection and to prevent HIV-infection in children at-risk?

Taking into account the approved 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.

Groups at high-risk of HIV infection also exist in the adolescent age range, hence it is worthwhile to consider pharmacological approaches as one component of the HIV prevention armamentarium also in adolescents.

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

For the treatment of HIV-1 infection at present, several therapies are available for the treatment of HIV-1 infection in children in the EU. These include several other NRTIs, including both individual active substances of the Truvada fixed-dose combination. The added convenience of fixed-dose combinations is in principle highly relevant to children of all ages just as for adults. However, due to its bone and renal toxicity in the EU tenofovir disoproxil fumarate is only authorised in paediatric patients who cannot take first-line agents due to NRTI resistance or toxicities. Therefore, the Committee considered that Truvada is not of the highest priority in the paediatric population.

Nevertheless, the Committee noted that Truvada is used off-label in adolescents, and that this use should be brought on-label through the agreement and completion of a paediatric investigation plan.

The Committee agreed that the adult film-coated tablet is suitable for use in adolescents and that no new paediatric clinical data have to be generated to support regulatory approval of the use of Truvada for the treatment of HIV-1 infection in adolescents, as the individual active substances are already authorised in this age group.

For the prevention of HIV-1 infection: at present, no treatment is authorised for PrEP to reduce the risk of sexually acquired HIV-1 infection in adolescents in the EU. The Committee considered that the use of Truvada for PrEP in adolescents could be supported by an extrapolation approach. However,

considering the known risks of Truvada (bone and renal toxicity) the Committee requested that the extrapolation study should also take into account safety data from young (aged 18-22 years), uninfected adults.

In addition, the Committee noted that clinical studies in PrEP in adolescents are being conducted by third parties, and that data from these studies should become available in the near future. The Committee therefore strongly recommends that the applicant supports their extrapolation study with safety data from these studies, when applying for an authorisation of PrEP in adolescents.

In order not to delay the availability of the medicine for PrEP in adults, given the late submission of this paediatric investigation plan, the Committee agreed with the request of the applicant that the extrapolation study should be deferred.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that for the treatment of HIV-1 infection:

- development of Truvada is not necessary in children below 12 years of age, as the product is not of high priority due to the restriction of tenofovir disoproxil fumarate to second line in children and adolescents due to its bone and renal toxicity;
- for the development in adolescents from 12 to less than 18 years of age, clinical studies in adolescents are not necessary because both active substances are already individually authorised in adolescents;
- the use of Truvada in adolescents will be supported by a completed study in healthy adult volunteers, that showed that the tablet containing both substances is absorbed in the body in the same way as the separate tablets given concurrently under similar conditions.

The Paediatric Committee considered that for the prevention of HIV-1 infection:

- development of Truvada is not necessary in children from 6 weeks to less than 12 years of age, as these children are not considered of high risk of sexually acquiring HIV, and in neonates and infants below 6 weeks of age, as Truvada is not of interest for the prevention-of-mother-to-child-transmission due to its safety profile;
- extrapolation of adult data on efficacy from uninfected adults and/or infected adolescents to uninfected adolescents, is possible in the development of this product, but should be supported by clinical data on the safety of PrEP in young adults and in adolescents from ongoing clinical studies conducted by third parties.

What happens next?

The applicant has now received the EMA Decision (P/0294/2015)* 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 December 2016.

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).