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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Dasabuvir/ombitasvir/paritaprevir/ritonavir for the treatment of chronic hepatitis C

On 11 September 2015, the Paediatric Committee of the European Medicines Agency agreed a product-specific waiver* for dasabuvir/ombitasvir/paritaprevir/ritonavir for the treatment of chronic hepatitis C (EMEA-001805-PIP01-15).

What is dasabuvir / ombitasvir / paritaprevir / ritonavir, and how is it expected to work?

The fixed-dose combination of dasabuvir/ombitasvir/paritaprevir/ritonavir is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the "treatment of genotype (GT) 1 chronic hepatitis C virus infection, including in patients with cirrhosis or liver transplant recipients".

Dasabuvir/ombitasvir/paritaprevir/ritonavir is a fixed-dose combination of 4 active substances, which work in different ways. Dasabuvir works by blocking the action of a protein in the hepatitis C virus called 'NS5B RNA-dependent polymerase', ombitasvir blocks the action of another protein called 'NS5A', and paritaprevir blocks the action of a third protein called 'NS3/4A protease'. Hepatitis C virus needs all of these three proteins to multiply. By blocking these proteins the medicine therefore prevents the virus from multiplying and infecting new cells. The fourth active substance, ritonavir, does not act directly against the hepatitis C virus but it slows down the removal of paritaprevir from the body, allowing paritaprevir to act against the virus for a longer time.

Dasabuvir has been authorised in adults since 15/01/2015 as Exviera and is normally taken together with a fixed-dose combination of ombitasvir/paritaprevir/ritonavir, which has also been authorised in adults since 15/01/2015 as Viekirax. Both Exviera and Viekirax have a paediatric investigation plan agreed to develop the medicines for the treatment of chronic hepatitis C in children from 3 to less than 18 years of age.

What was the proposal from the applicant?

For children, the applicant proposed not to do any study in children (from birth to less than 18 years of age), because the dose, safety and efficacy of dasabuvir, ombitasvir, paritaprevir and ritonavir are

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already being determined in children from 3 to less than 18 years of age in the clinical studies conducted with the individual products Vikierax and Exviera as part of the PIPs agreed for these products. Below 3 years of age treatment of chronic hepatitis C is not normally considered necessary.

Therefore the applicant only proposed an extrapolation study to support the use of the adult tablet in adolescents.

The applicant proposed a deferral* for the extrapolation study.

Is there a need to treat children affected by chronic hepatitis C?

Chronic hepatitis C occurs also in children, who can be infected from their mothers at birth. However, a significant proportion of children infected at birth can clear the infection in the first years of life without treatment, and even in those that do not clear the virus the disease progresses only slowly. Therefore, treatment is not normally considered necessary for children below 3 years of age.

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

For adolescents, the Committee considered that no data are needed for this fixed-dose combination, as data on the dose, safety and efficacy of the 4 active substances are already being collected with the individual products Exviera and Vikierax. In addition, the applicant will confirm in adults that the active substances in the combined tablet are absorbed by the body in the same way as the two medicines (Exviera and Vikierax) given separately. Provided this is confirmed, and the studies with the individual products confirm that adolescents can use the adult dose, adolescents (from 12 to less than 18 years of age) will be able to use the adult tablet without the need for a formal extrapolation study.

For children from 3 years to less than 12 years of age, in principle fixed-dose combinations are of interest in the treatment of chronic hepatitis C. However, in this specific case the Committee considered that, due to the complex regimen with 4 active substances, the medical needs of this age group are better served by the age-appropriate formulations of the individual products, which will allow greater flexibility in dosing. The applicant is legally obliged to develop these age-appropriate formulations within the agreed paediatric investigation plans for Exviera and Vikierax. Therefore, exceptionally, a waiver for dasabuvir/ombitasvir/paritaprevir/ritonavir was considered acceptable in this age range.

For children below three years of age, the Committee agreed with the applicant that studies are not needed, because treatment is not normally considered necessary in this age group due to the slow disease progression and high rate of spontaneous clearance of the virus.

What is the content of the Plan after evaluation?

The Paediatric Committee granted an exemption (waiver*) from conducting studies in the whole paediatric age range (from birth to less than 18 years of age), but noted that this waiver should not discourage the applicant from seeking authorisation of the fixed-dose combination in adolescents, if appropriate.

What happens next?

The applicant has now received the EMA Decision (P/0228/2015)* 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 adolescents, if appropriate).

*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).