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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Grazoprevir/elbasvir for the treatment of chronic hepatitis C

On 12 December 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for grazoprevir/elbasvir for the treatment of chronic hepatitis C (EMEA-001604-PIP01-13).

On 13 November 2015, the Paediatric Committee of the European Medicines Agency agreed on some modifications to this paediatric investigation plan. See last paragraph “Subsequent modifications of the agreed Paediatric Investigation Plan” of this document (EMEA-001604-PIP01-13-M01).

What is grazoprevir/elbasvir, and how is it expected to work?

Grazoprevir/elbasvir cis a combination of two active substances. Elbasvir blocks the action of a viral protein called ‘NS5A’ and grazoprevir blocks the action of a viral protein called ‘NS3/4A protease’. These two proteins are essential for HCV to multiply. By inhibiting these two proteins, grazoprevir/elbasvir stop the virus from multiplying and infecting new cells.

The combination grazoprevir/elbasvir is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the treatment of chronic hepatitis C (CHC) genotypes 1, 4 and 6 infection.

What was the proposal from the applicant?

For children, the applicant proposed:

to study the medicine in adolescents from 12 years to less than 18 years of age with chronic GT 1, 4 or 6 HCV infection, who are either treatment-naïve or who have received prior HCV therapy, in a paediatric investigation plan*.
The proposed future indication for children is: grazoprevir/elbasvir is indicated for the treatment of chronic hepatitis C (CHC) infection genotypes 1, 4 and 6. The plan includes the development of a specific pharmaceutical form to be used in children*. It also includes a proposal to determine the right dose and to show antiviral activity and safety of the medicine in clinical studies.
The applicant proposed a deferral* for the clinical studies.

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Is there a need to treat children affected by the disease?

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 chronic hepatitis C in children. This condition 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?

At present, some treatments are available for the treatment of chronic hepatitis C in children in the European Union, such as peginterferon alfa-2a or peginterferon alfa-2b in combination with ribavirin, but these treatment regimens may cause serious side effects and are not well tolerated by many patients.

Therefore, there is a need for more medicines for the treatment of chronic hepatitis C in children. Grazoprevir/elbasvir has a potential interest for children, however, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to the children affected by the condition, and to understand any potential risks.

The Committee considered that this medicinal product would be of interest also in children younger than 12 years of age and that there is hence also a need to develop an age-appropriate 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.

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 children below 3 years of age 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.
- An age-appropriate pharmaceutical form* was needed for children unable to swallow the film-coated tablet. This age-appropriate pharmaceutical form (granules) will be developed by the applicant.
- Determination of the best dose should be done in a study of the medicine's behaviour in the body.
- It is necessary to show efficacy to treat the disease in children. This will be done by assessing antiviral activity in a single-arm study.
- It is also necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur.

What happens next?

The applicant has received the EMA Decision (P/0024/2015)* 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 December 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 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.

Subsequent modifications of the agreed Paediatric Investigation Plan

On 21 August 2015, Merck Sharp & Dohme (Europe), Inc. proposed to change some of the details of the previously agreed Plan.

The Paediatric Committee, after examining the request, agreed to modify the following details:

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- Details in the clinical measure(s) have been modified to include the use of the adult fixed-dose combination tablet in adolescents (weighing at least 35 kg), as this will accelerate initiation of the paediatric clinical study. In addition a secondary PK endpoint was deleted, as the determination of this parameter would require an undesirable dose interruption.

An updated Decision on the Plan has therefore been published on the EMA website (P/0314/2015).

*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).