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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide (VX-661) / ivacaftor for treatment of cystic fibrosis

The Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for the medicines reported above for the treatment of cystic fibrosis (EMEA-001640-PIP01-14).

What is 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide (VX-661) / ivacaftor, and how is it expected to work?

This medicine targets the basic defect of cystic fibrosis by improving the CFTR (cystic fibrosis conductance regulator) mediated chloride ion secretion and is expected to improve the pulmonary (lung) and extra-pulmonary manifestations of CF, prevent progressive lung damage, and prolong survival in subjects with CF who have at least one allele of the F508del CFTR mutation, the most common mutation in the CFTR gene.

This medicine is proposed for the treatment of cystic fibrosis in patients with cystic fibrosis but is not yet authorised anywhere in the world. Studies in adults and in children are currently on-going.

What was the proposal from the applicant?

The applicant proposed to study the medicine in children from birth to 18 years of age affected by cystic fibrosis as part of a paediatric investigation plan*. The plan included the development of a specific pharmaceutical form to be used in children* (tablet; age appropriate oral formulation for children less than 6 years of age). It also includes a proposal to determine the right dose and to show efficacy and safety of the medicine in non-clinical and clinical studies and trials.

Is there a need to treat children affected by cystic fibrosis?

This disease affects children from birth onwards as well as adults. Therefore, taking into account the characteristics of the medicine, the Paediatric Committee considered this medicine was of potential use for the treatment of cystic fibrosis in children of all age groups, including newborns.

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

At present no treatment that target the basic defect in persons with the F508del CFTR mutation, is authorised for this population in the European Union. Therefore, the Committee considered that data were necessary 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 there was 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 (age appropriate oral formulation), which composition* must only include components that are known to be safe in children.

Because there is a need for more medicines to treat children affected by cystic fibrosis, and this medicine has a potential interest for children, the Committee considered that pre-clinical and clinical studies were necessary.

What is the content of the Plan after evaluation?

The Committee considered that:

- as cystic fibrosis affects neonates, one clinical study including children from birth to less than 2 years of age will be performed in this age group to obtain the necessary data.
- An age appropriate pharmaceutical form* was needed for newborns and children below 6 years of age. An oral formulation will be developed by the applicant.
- Determination of the best dose should be made with three studies of the medicines behaviour in the body.
- It is necessary to show efficacy to treat the disease in children. This will be done in four studies comparing the medicine to placebo.
- It is necessary to study the potential side effects and the long-term safety of the medicine, to prevent them or to reduce the consequences if they occur. This will be done in three more studies.

What happens next?

The applicant has now received the EMA Decision (P/0098/2015)* 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 2024.

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).