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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Dapagliflozin (Forxiga) for the treatment of type 1 diabetes mellitus

On 13 February 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for dapagliflozin (Forxiga) for the treatment of type 1 diabetes mellitus (EMEA-000694-PIP02-14).

On 29 January 2016, 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-000694-PIP02-14-M01).

What is dapagliflozin (Forxiga), and how is it expected to work?

Dapagliflozin (Forxiga) is a medicine currently authorised in adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy, when diet and exercise alone do not provide adequate blood sugar (glycaemic) control in patients for whom use of metformin is considered inappropriate due to intolerance; and as add-on combination therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate blood sugar control.

Its safety and efficacy have not yet been studied in children.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 2 years to less than 18 years of age affected by type 1 diabetes mellitus, in a paediatric investigation plan*.

The future indication proposed for children is: to improve glycaemic control in combination with insulin, when insulin does not provide adequate glycaemic control in children with type 1 diabetes mellitus. The plan includes the development of a specific age appropriate oral dosage form 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.

The applicant proposed a deferral* for the development of the specific pharmaceutical form to be used in children and for paediatric clinical studies.

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Is there a need to treat children affected by type 1 diabetes mellitus?

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 type 1 diabetes mellitus. This condition occurs also in children, and affects infants and toddlers, preadolescent children and adolescents.

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

At present, only insulin is available for the treatment of type 1 diabetes mellitus in children in the European Union. While insulin is an effective glucose lowering medication, its limitations include the potential for hypoglycaemia (when blood sugar drops to a dangerous level), weight gain, and fluctuations in blood glucose levels. Even with more intensive insulin regimens, many children and adolescents do not achieve on insulin their target blood sugar levels. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will improve the blood sugar profile in patients inadequately controlled on an intensive insulin regimen and thus will bring a benefit to children from 2 years to less than 18 years affected by the condition, and to understand any potential risks.

The Committee considered that there is also a need to develop a specific age-appropriate oral 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 type 1 diabetes mellitus in children, and this medicine has a potential interest for children, the Committee considered that clinical studies were necessary.

The Committee agreed on the development of a specific age-appropriate oral dosage form for use in younger children and paediatric clinical studies should be deferred to avoid a delay in the availability of the medicine for adults.

The Committee confirmed that there could be a potential use of this product in children from the age of 2 years and older. Dapagliflozin should not be given to children younger than 2 years of age as juvenile and pre- and postnatal development studies in rats showed some changes in the animals' kidneys, which could constitute potential risk for the kidney maturation in children less than 2 years of age.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- An age appropriate oral pharmaceutical form* was needed for children aged from 2 years to less than 6 years of age that will be developed by the applicant.
- It is necessary to study if the medicine is effective to treat the disease in children. It is also necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. This will be done in 2 studies comparing the medicine plus insulin to placebo* plus insulin.

What happens next?

The applicant has received the EMA Decision (P/0064/2015)* 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 June 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 22 September 2015, AstraZeneca AB proposed to change some of the details of the previously agreed Plan.

EMEA-000694-PIP02-14-M01

- Details in the development of a formulation to be used in children have been modified.

An updated Decision on the Plan has therefore been published on the EMA website (P/0063/2016).

*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).