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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Mirabegron for the treatment of neurogenic detrusor overactivity

On 17 April 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for mirabegron for the treatment of neurogenic detrusor overactivity (EMEA-000597-PIP03-15).

EMEA-000597-PIP03-15 was agreed as the applicant requested to include the condition "treatment of neurogenic detrusor overactivity" in a separate PIP, having previously been included in EMEA-000597-PIP02-10 together with the condition "treatment of idiopathic overactive bladder". By doing so the two conditions have been separated into two individual PIPs, which may have regulatory advantages for the applicant.

On 9 October 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-000597-PIP03-15-M01).

What is Betmiga / mirabegron, and how is it expected to work?

Betmiga / mirabegron is a medicine currently authorised in adults for the symptomatic treatment of urgency, increased frequency of urination and/or incontinence as may occur in patients with the "overactive bladder" (OAB) syndrome. Its safety and efficacy have not yet been studied in children.

The active substance in Betmiga, mirabegron, is a beta-3-adrenergic-receptor agonist. It works by attaching to and activating beta-3 receptors that are found in the muscle cells of the bladder. This medicine is expected to cause the bladder muscles to relax. This is thought to lead to an increase in the capacity of the bladder and to changes in the way the bladder contracts, resulting in fewer bladder contractions and thus fewer unwanted urinations.

What was the proposal from the applicant?

In the first PIP application (EMEA-000597-PIP01-09) the applicant proposed to do studies only in children from 6 years of age with idiopathic overactive bladder. However, the first PIP application was withdrawn. Subsequently the applicant proposed to study the medicine in children from 6 months to less than 18 years of age affected by neurogenic detrusor overactivity, in a paediatric investigation plan*. The future indication proposed for children is: Treatment of detrusor overactivity in children

with neurogenic bladder dysfunction. The plan includes the development of specific pharmaceutical forms to be used in children*: a prolonged-release microgranula-based suspension with a compatible delivery device and a prolonged-release tablet. 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.

The applicant requested a deferral* for the development of specific pharmaceutical forms to be used in children and for non-clinical and paediatric clinical studies.

Is there a need to treat children affected by neurogenic detrusor overactivity?

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 neurogenic detrusor overactivity. This condition predominantly occurs in children. Moreover, this medicine is also considered to be of potential use for the treatment of idiopathic overactive bladder in children. However, this separate condition is included in EMEA-000597-PIP02-10.

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 neurogenic detrusor overactivity in children in the European Union, such as antimuscarinic agents. However, these are only authorised for use in children from 5 years of age, and are associated with certain tolerability problems. Therefore, the Committee considered that new data are required to decide whether the use of mirabegron will bring a benefit to children from 6 months to less than 18 years of age affected by the condition, and to understand any potential risks.

The Committee considered that there is 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, 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 neurogenic detrusor overactivity in children, and mirabegron has a potential interest for children, the Committee considered that non-clinical and clinical studies were necessary.

The Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults, before starting the paediatric studies.

The Committee agreed with the request of the applicant that the development of specific pharmaceutical forms to be used in children, non-clinical and paediatric clinical studies should be deferred to avoid a delay in the availability of the medicine for adults.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in children from birth to less than 6 months of age, because the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.
- Pharmaceutical forms* such as an oral age-appropriate prolonged-release microgranula-based suspension with a compatible delivery device and a prolonged-release tablet were needed for children aged from 6 months to less than 18 years of age.

- Studies in animals need to be performed, to identify any risk before the medicine is used in infants and neonates / young children.
- Determination of the best dose should be done with 4 clinical trials of the medicine's behaviour in the body.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in 1 study comparing the efficacy of the medicine to that of an active control*.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. The main concern identified by the PDCO is the potential toxicity of the medicine for heart and liver.

What happens next?

The applicant has now received the EMA Decision (P/0117/2015)* on this medicine. The Decision itself is necessary for the applicant to 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 by 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.

Subsequent modifications of the agreed Paediatric Investigation Plan

On 20 July 2015, Astellas Pharma Europe B.V. 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:

EMEA-000597-PIP03-15-M01

- Details in the clinical measure(s) have been modified (changes of study design in line with current guidelines and in order to facilitate timely conduct).

An updated Decision on the Plan has therefore been published on the EMA website (P/0269/2015).

*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).