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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Belimumab for treatment of systemic lupus erythematosus

1. Evaluation of the initial application for a Paediatric Investigation Plan

1.1. Procedure

On 12 September 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for Belimumab for treatment of systemic lupus erythematosus (EMEA-000520-PIP02-13).

1.2. What is Benlysta / Belimumab and how is it expected to work?

Benlysta / Belimumab is authorised in the European Union. Belimumab is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.

Studies in children are currently on-going.

Belimumab is a monoclonal antibody. Belimumab has been designed to attach to and block a protein called BLyS which helps B lymphocytes to live longer. By blocking the action of BLyS, belimumab reduces the life span of B lymphocytes, thereby reducing the inflammation and organ damage that occur in systemic lupus erythematosus (SLE).

1.3. What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 5 years to less than 18 years of age affected by SLE, in a paediatric investigation plan*. The future indication proposed for children is: treatment of SLE. The plan includes a proposal to show efficacy and safety of the medicine in clinical studies.

The applicant proposed a deferral* for the paediatric clinical studies.

1.4. Is there a need to treat children affected by systemic lupus erythematosus?

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 SLE. This condition occurs also in children.

1.5. 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 SLE in children in the European Union, such as corticosteroids, anti-malarial agents, NSAIDs, cytotoxic agents, and immunosuppressive / immunomodulatory agents. Most of these therapies can be associated with significant toxicity. The Paediatric Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from 5 to less than 18 years affected by the condition, and to understand any potential risks.

Because there is a need for more medicines for the treatment of SLE in children, and this medicine has a potential interest for children, the Paediatric Committee considered that 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. Therefore, the Paediatric Committee agreed with the request of the applicant that the paediatric clinical studies should be deferred.

1.6. What is the content of the agreed Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in children below 5 years of age because SLE does not occur in this age group.
- It is necessary to determine of the best dose in the paediatric population. This will be done with one trial of the medicine's behaviour in the body and the body's reactions to it. The dose for use of for belimumab in the paediatric population (from 5 to less than 18 years of age) for solution for injection for subcutaneous use will be selected to match the pharmacokinetic exposures of the effective dose of belimumab powder for concentrate for solution for infusion for intravenous use.
- It is necessary to study if the medicine is efficacious to treat the disease in children as differences in the disease exist between adults and children. Compared with adult SLE patients, children with SLE have more active disease both at the time of diagnosis and over time. The efficacy and safety evaluation will be done in one pivotal paediatric clinical study, comparing the medicine to placebo* in an add-on to standard of care setting. This study will be the same as the study done for the paediatric development for the powder for concentrate for solution for infusion for intravenous use.

It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. The Paediatric Committee considered that the following issues are particular causes of concern in paediatric population: potential occurrence of autoimmune diseases, infections and malignancies as well as immunogenicity.

1.7. What happens next?

The applicant has now received the EMA Decision* (P/0276/2014) 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 will perform the studies and trials 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 May 2023.

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 efficacious 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.

2. Subsequent modifications of the agreed Paediatric Investigation Plan

2.1. Modification n. 1, EMEA-000510-PIP02-13-M01

On 24 November 2014, Glaxo Group Limited 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:

- Timelines: Date of completion of one clinical study has been postponed by 2 years due to slow recruitment.
- Details in the clinical measure(s) have been modified as the eligibility criteria were modified to facilitate recruitment.

An updated Decision on the Plan has therefore been published on the EMA website (P/0063/2015).

*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).