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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Anti programmed death-ligand 1 (PD-L1) monoclonal antibody (MPDL3280A) for treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms)

On 13 February 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for anti-programmed death-ligand 1 (PD-L1) monoclonal antibody (MPDL3280A)for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (EMEA-001638-PIP01-14).

What is MPDL3280A and how is it expected to work?

MPDL3280A is not authorised in the European Union. Studies in adults and children are currently on-going. This medicine is proposed in adults for the treatment of:

- Patients with locally advanced or metastatic non-small lung cell lung carcinoma that is PD-L1 positive, after failure of a platinum containing chemotherapy regimen;
- Patients with inoperable locally advanced or metastatic urothelial bladder carcinoma that is PD-L1 positive, after failure of a platinum containing chemotherapy regimen;
- Patients with metastatic renal cell carcinoma in combination with bevacizumab.

This medicine is a monoclonal antibody (a type of protein) expected to attach to and block the activity of a protein called PD-L1 that is found on the surface of tumour cells and of tumour-infiltrating immune cells. MPDL3280A prevents binding of PD-L1 to PD-1 and B7.1 expressed on the surface of T cells, a type of white blood cells. PD-L1 inhibits the activity of T cells and MPDL3280A, by blocking PD-L1, thus leading to activation and spread of the T cells, that infiltrate tumours and kill the tumour cells.

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What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 6 months to less than 18 years of age affected by all conditions included in the category of malignant neoplasms (except hematopoietic and lymphoid tissue) with known or expected PD-L1 pathway, in a paediatric investigation plan*.

The future indication proposed for children: treatment of children with solid tumours with known or expected PD-L1 pathway involvement.

The plan included a proposal to determine the right dose and to show efficacy and safety of the medicine clinical studies.

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

Is there a need to treat children affected by all conditions included in the category of malignant neoplasms?

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 all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms). This condition occurs in all age subset and includes several types of solid tumours that may affect in particular infants and toddlers, or preadolescent children or adolescents. The type of solid tumours proposed for the adult indications occur most often (e.g. renal cell carcinoma) or almost exclusively (e.g. non-small cell lung carcinoma) in adults.

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

At present, some treatments are available for some of the tumours comprised in the conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) in children in the European Union. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from birth 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 conditions included in the category of malignant neoplasms in children, and this medicine has a potential interest for children, the Committee considered that non-clinical and clinical studies were necessary.

The Committee considered that the condition is serious enough in children, and that there are no satisfactory enough treatments available for children yet. Consequently, studies with children should start and be completed without waiting for all the results of studies in adults.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- As disease affects also neonates, 2 clinical studies including children from birth to less than 18 years of age will be performed to obtain the necessary data.
- Studies in paediatric tumour tissues need to be performed, to identify PD-L1 expression on paediatric tumour cells to inform how to best study the medicine is children.

- Determination of the best dose should be done with one trial of the medicine's behaviour in the body and the body's reactions to it.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in one study comparing the medicine to best known active standard of care determined by tumour type.
- 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 immune system.

What happens next?

The applicant has now received the EMA Decision (P/0076/2015)* 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 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 June 2025.

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).