05 July 2016
EMA/251728/2016
Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Fluciclovine (18F) for diagnosis of amino acid metabolism in solid malignant tumours

On 11 September 2015 the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for fluciclovine (18F) for the diagnosis of amino acid metabolism in solid malignant tumours (EMEA-001644-PIP02-14).

What is fluciclovine (18F) and how is it expected to work?

Fluciclovine (18F) is a medicine currently not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the Diagnosis of prostate cancer and Diagnosis of primary and recurrent brain tumours.

This medicine is a diagnostic radiopharmaceutical, an analogue of the amino acid leucine, labelled with 18F (fluoride-18), which is a radioactive form of the chemical element fluorine. When fluciclovine (18F) is injected in the body, the radiolabelled fluciclovine is absorbed in the same way as leucine. This is done particularly actively by cells of prostate cancer and glioma, a type of tumour of the central nervous system. Once in the tumour cells, the radioactivity remains trapped, and can be seen on scans such as those obtained using a 'PET' (positron emission tomography) scanner providing better diagnosis of the tumours mentioned above.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 1 year to less than 18 years of age affected by solid malignant tumours in a paediatric investigation plan*. The future indication proposed for children is: Diagnosis of primary and recurrent brain tumours in children. The plan includes a proposal to determine the right dose, to show efficacy and safety of the medicine in a clinical study and to extrapolate data from studies in adults.

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

The applicant requested an exemption (waiver*) from the obligation to study the medicine in children from birth to less than 1 year of age in the condition diagnosis of amino acid metabolism in solid malignant tumours.

Is there a need to diagnose children affected by solid malignant tumours?

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 diagnosis of amino acid metabolism in solid malignant tumours, particularly in gliomas. This condition occurs predominantly in children and affects in particular infants and children less than 5 years of age.

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

The Committee disagreed with the request of the applicant to be exempt from performing studies in children from birth to less than 1 year of age, since the medicinal product may be useful for diagnosis of amino acid metabolism in solid malignant tumours in this age group. The Committee considered that safety concerns are not related to the age but to the appropriate radioactivity dose for administration. Consequently, the applicant was invited to include also this age group in the proposed paediatric investigation plan.

At present, some tests are available for the diagnosis of solid malignant tumours in children in the European Union, such as MRI (magnetic resonance imaging) and CT (computed tomography) scan with and without contrast or FDG (fludeoxyglucose 18F) PET scan that are known to be effective for diagnosis of solid malignant tumours. The Committee considered that new data are required to decide whether the use of fluciclovine (18F) will bring a benefit to children from birth to less than 18 years of age affected by the condition, and to understand any potential risks.

Because there is a need for more medicines for the diagnosis of amino acid metabolism in solid malignant tumours in children, and this medicine has a potential interest for children, the 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.

The Committee agreed with the request of the applicant that the paediatric clinical and extrapolation 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:

- Determination of the best dose should be done with 1 trial of the medicine's behaviour in the body.
- It is necessary to study if the medicine is effective to diagnose the disease in children. This will be done in 1 study comparing fluciclovine (18F) PET scan to MRI.
- 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 cancer risk associated with radiation exposure.
- Partial extrapolation of diagnostic performance of fluciclovine (18F) is possible in the development of this product, between adults and children due to similarities of disease and the probable similarities in uptake and distribution of fluciclovine (18F) by tissues in adults and children.

What happens next?

The applicant has now received the EMA Decision (P/0256/2015)* 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 December 2019.

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	The physical aspect of the medicine (the form in which it is presented), for

form	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).