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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed product-specific waiver

Ezetimibe / atorvastatin (calcium trihydrate) for the prevention of coronary artery disease

On 20 March 2015, the Paediatric Committee of the European Medicines Agency agreed a product-specific waiver* for ezetimibe / atorvastatin (calcium trihydrate) for the prevention of coronary artery disease (EMEA-001204-PIP02-14).

What is Atozet, Kexrolt, Orvatez, Tioblis and associated names (ezetimibe / atorvastatin (calcium trihydrate)), and how is it expected to work?

Atozet is a medicine currently authorised in adults for the treatment of hypercholesterolaemia and for the treatment of homozygous familial hypercholesterolaemia (HoFH). Its safety and efficacy have not been studied in children.

This medicine is a fixed dose combination of ezetimibe (a lipid-lowering compound) and atorvastatin (a cholesterol-lowering compound) expected to reduce cholesterol in two ways. Ezetimibe reduces the cholesterol absorbed in the digestive tract and atorvastatin inhibits cholesterol produced by the body. By reducing cholesterol level Atozet is expected to reduce the risk of coronary artery disease, a result of cholesterol laden plaque build-up in coronary arteries.

What was the proposal from the applicant?

For children, the applicant proposed:

Not to do any study in children (from birth to less than 18 years of age), because of lack of expected significant therapeutic benefit of the fixed dose formulation versus the individual components. Therefore, the applicant requested an exemption (waiver*) from the obligation to study the medicine in any children, in the condition prevention of coronary artery disease.

Is there a need to treat children at risk of coronary artery disease?

Coronary artery disease is extremely rare in children and usually manifests in later adulthood. The pathologic process of plaque build-up in arteries potentially leading to coronary artery disease can

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begin in children with hypercholesterolemia or other risk factors. Therefore, treatment in childhood in order to prevent coronary artery disease later in life could be of benefit.

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

The Committee agreed with the request of the applicant to be exempt from performing studies in children from birth to less than 18 years, because the Committee concluded that clinical studies with this medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population.

The Committee came to this conclusion because each mono-component has been already authorised for the treatment of hypercholesterolaemia and hyperlipidaemia in adults and children respectively. Therefore, additional clinical trials in children in this rather rare condition are not justified. Moreover, the ability to titrate pharmacological therapy for the treatment in paediatric patients with this condition is important. This flexibility would not available with a fixed dose combination.

What happens next?

The applicant has now received the EMA Decision (P/0079/2015)* 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*.

*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).