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Human Medicines Research and Development Support Division

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

Hydromorphone (hydrochloride) / naloxone (hydrochloride) for treatment of pain and opioid-induced constipation

On 14 August 2014, the Paediatric Committee of the European Medicines Agency agreed a product-specific waiver* for hydromorphone (hydrochloride) / naloxone (hydrochloride) for treatment of pain and opioid-induced constipation (EMEA-001762-PIP01-15).

What is hydromorphone (hydrochloride) / naloxone (hydrochloride), and how is it expected to work?

This medicine is a combination of hydromorphone (hydrochloride), an opioid analgesic and naloxone (hydrochloride) which is an opioid receptor antagonist that is added to counteract opioid-induced constipation (OIC) which is a common safety concern of opioid use. This combination is not currently authorised is not authorised in the European Union and its safety and efficacy have not been studied in children.

Studies in adults are currently on-going. This medicine is proposed in adults for severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation (OIC) by blocking the action of hydromorphone at opioid receptors locally in the gut.

What was the proposal from the applicant?

The applicant proposed not to do any study in children (from birth to less than 18 years of age), because in the treatment of pain and opioid induced constipation such combination is not considered to have any new therapeutic benefit for children as this fix dose combination is not readily adaptable to paediatric needs in terms of pain control and is likely to be unsafe in younger children. Therefore, the applicant requested an exemption (waiver*) from the obligation to study the medicine in any children.

Is there a need to treat children affected by pain and opioid induced constipation?

The Committee recognises that there is a need to treat pain and in some cases opioid induced constipation in the paediatric population. Taking into account the proposed indication in adults, and

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the characteristics of the medicine, however, the Paediatric Committee considered this medicine was not of potential use for the pain and opioid induced constipation in the paediatric population.

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

The PDCO, agreed with the request of the applicant to be exempted from performing studies in children from birth to less than 18 years old, since the individual components do not have yet both an established clinical benefit. Moreover modified release opioids are generally considered not suitable for children due to risk of overdose and difficulties in titrating the dose. In the younger patients there is potential risk of overdose and the medicinal product could be unsafe and in older ones the specific fixed dose combination does not represent a significant therapeutic benefit over existing treatments in the treatment of pain and opioid induced constipation.

What happens next?

The applicant has now received the EMA Decision (P/0223/2015)* on this medicine. The Decision itself is necessary for the applicant to request in the future a marketing authorisation* for this medicine in adults.

*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).