European Medicines Agency

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Questions and answers on the withdrawal of the marketing application for Ramelteon

International non-proprietary name (INN): ***ramelteon***

On 19 September 2008, Takeda Global Research & Development Centre (Europe) Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Ramelteon, for the treatment of primary insomnia in adult patients.

What is Ramelteon?
Ramelteon is a medicine that contains the active substance ramelteon. It was to be available as tablets.

What was Ramelteon expected to be used for?
Ramelteon was expected to be used to treat primary insomnia (difficulty falling and staying asleep, and poor quality of sleep) in patients aged 18 years or over. 'Primary' means that the insomnia does not have any identified cause, including other medical, mental or environmental causes.

How is Ramelteon expected to work?
The active substance in Ramelteon, ramelteon, is a melatonin-receptor agonist. This means that it works by attaching itself to the receptors that melatonin normally attaches to. Melatonin is a naturally occurring hormone that is involved in co-ordinating the body's sleep cycle by acting on receptors in specific areas of the brain. Ramelteon was expected to work in the same way as melatonin in promoting sleep.

What documentation did the company present to support its application to the CHMP?
The effects of Ramelteon were first tested in experimental models before being studied in humans. The effectiveness of Ramelteon was compared with that of placebo (a dummy treatment) in a total of about 5,400 patients. Most of the studies were carried out in sleep laboratories, but the three main studies were carried out in the 'natural setting' (at home) in a total of 2,807 patients.
All of the studies but one were short-term, lasting five weeks or less. The one long-term study lasted six months, during which patients spent some nights in a sleep laboratory. The main measure of effectiveness was the time taken for the patients to fall asleep.

How far into the evaluation was the application when it was withdrawn?
The evaluation had finished and the CHMP had given a negative opinion. The company had requested a re-examination of the negative opinion, but this had not yet finished when the company withdrew.

What was the recommendation of the CHMP at that time?
Based on the review of the data and the company's response to the CHMP list of questions, at the time of the withdrawal, the CHMP had given a negative opinion and did not recommend a marketing authorisation for Ramelteon for the treatment of primary insomnia in adult patients.

What were the main concerns of the CHMP?
The CHMP was concerned that the company had not demonstrated the effectiveness of Ramelteon, which was measured by looking at only one aspect of insomnia, the time to fall asleep. In addition, in

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only one of the three studies carried out in the natural setting was there a difference in the time taken to fall asleep between patients taking Ramelteon and those taking placebo. This difference was considered to be too small to be relevant. When other aspects of sleep were considered, Ramelteon did not have any effect. The Committee was also concerned that the company had not demonstrated the long-term effectiveness of Ramelteon.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Ramelteon had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.

What were the reasons given by the company to withdraw the application?
The letter from the company notifying the EMEA of the withdrawal of the application is available here.

What are the consequences of the withdrawal for patients in clinical trials or compassionate use programmes using Ramelteon?
The company informed the CHMP that there are no ongoing clinical trials or compassionate use programs with Ramelteon in the European Union.